New approaches towards treatment of insomnia

Sleep is a cyclical process consisting of two stages: Non-Rapid Eye Movement (NREM) and Rapid Eye Movement (REM). NREM is divided into light (stage 1 and 2) and slow wave sleep (stage 3 and 4). Several neurotransmitters control the sleep process including: serotonin, noradrenaline, dopamine, histamine, hypocretin, acetylcholine, GABA and galanine. Absence of sleep stages and cycle is associated with insomnia. Elderly and women are more prone to have insomnia. Other associated factors include medical conditions, taking certain medications, physiological factors, chronobiological factors social factors such as divorce and being widowed and behavioural factors. Insomnia, if not treated, may result in depression, anxiety, obesity, diabetes and impaired glucose tolerance, increased susceptibility to pathogens, compromised work productivity and increased risk of accidents. Current pharmacological treatments include benzodiazepines and newer benzodiazepine-like agents including zolpidem and zaleplon, ethanol, antihistamines, exogenous melatonin, chloral hydrate, barbiturates and sedating anti-depressants. These drugs have several limitations that necessitate the development of new drugs for the treatment of insomnia.

Sleep cycle
Brain activity can be recorded by EEG during wakefulness and sleep (Fig 1). Light sleep referring to stages 1 and 2 shows a relatively low voltage with mixed frequency activity, while deep sleep referring to stages 3 and 4, which is also called slow-wave sleep, is characterized by increasing high voltage activity. In REM sleep brain activity resembles that of wakefulness. Healthy individuals may cycle between stages of NREM and REM throughout the night (1, 2).

The average length of the first NREM-REM sleep cycle is 70-100 min with 75-80% in NREM, and 20-25% in REM sleep. Stage 1 lasts 1-7 min (2-5 % of total sleep). Stage 2 lasts approximately 10-25 min constituting 45-55% of the total sleep. In this stage, an individual requires more intense stimuli than in stage 1 to awaken. Stage 3 lasts only a few minutes (3 to 8 % of sleep). Stage 4 of NREM lasts 20-40 min in the first cycle and constitutes 10-15% of sleep. Stages 3 and 4 are classified as the deepest stages of sleep (3,4).

REM sleep lasts only 1-5 min during the initial cycle, but is progressively prolonged as sleep progresses. Here, the brain appears to be as active as during wake periods (1); dreaming is associated with this state of sleep. Also, in REM sleep there is a loss of muscle tone and reflexes which is important to prevent the individuals from acting out their dreams while sleeping. REM sleep is important for memory consolidation (3).

Fig 1. Brain activity recorded by EEG. Adapted from http://sleepamongstspecies.wordpress.com

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Role of neurotransmitters

In the brainstem and posteriolateral hypothalamus, wake promoting neurotransmitters include serotonin (5-hydroxytryptamine, 5-HT), noradrenaline, dopamine, histamine, hypocretin and acetylcholine (Ach) (5). In the anterior hypothalamus, preoptic area and the adjacent basal forebrain, there are both wake promoting neurotransmitters, gamma-aminobutyric acid (GABA) and Ach, and sleep promoting neurotransmitters, GABA and galanine. The synthesis and the release of sleep promoting factors, such as interleukin 1 (IL-1), are induced by serotonin (5). These relationships are illustrated in Fig 2.

Factors associated with insomnia

About 10-30% of the general population suffer from insomnia. A persistent insomnia for more than 1 month, without the association of physical problem and mental disorder, is considered primary insomnia. Association with specific events, including periods of stress or anxiety, and linkage to other psy-

Figure 2. Serotonin effect in wakefulness and NREM sleep. ACh, acetylcholine; DA, dopamine; GABA, γ-aminobutyric acid; LC, locus coeruleus; LDT–PPT, laterodorsal and pedunculopontine tegmental nuclei; NA, noradrenaline; NREM, non-rapid eye movement; PeF, perifornical region; TMN, tuberomammillary nucleus; VTA, ventral tegmental area. Adapted from (5).
Insomnia is associated with psychiatric disorders (most commonly depression and anxiety) (8) more frequently than any other medical condition. Additionally, sleep loss increases obesity by increasing appetite. Sleep loss results in high levels of ghrelin (a peptide that stimulates appetite) and low levels of leptin (a hormone produced by adipose tissues that reduces appetite) (9). Other consequences of insomnia are diabetes and impaired glucose tolerance. Sleep loss can increase sympathetic activity leading to impairment of glucose regulation because of the lipolytic effects of adrenergic stimulation of visceral adipose tissue. The impact of sleep loss on glucose regulation suggests a mechanism whereby short sleep time might increase mortality (10).

Insomnia affects the immune system by impairing host defense mechanisms and increasing the susceptibility to viral and bacterial pathogens (11). Furthermore, insomnia can lead to impairment of learning, thinking, memory, perceptual skills, deterioration of mood, attention and concentration which may result in compromised work productivity.

**Current treatments of insomnia and their limitations**

Current pharmacological therapies include benzodiazepines, newer benzodiazepine-like agents including zolpidem and zaleplon, ethanol, antihistamines, exogenous melatonin, chloral hydrate, barbiturates, and sedating antidepressants.

**Benzodiazepines**

Benzodiazepines (used as anxiolytics, hypnotics or anticonvulsants) modulate GABA receptor function by enhancing GABA's inhibitory action in the brain (1, 12). The most commonly prescribed benzodiazepines are alprazolam (Xanax), clonazepam (Klonopin), diazepam (Valium), and lorazepam (Ativan); 1, 5-benzodiazepines have similar therapeutic properties as 1,4-benzodiazepines but with considerably less sedative and hypnotic activity.

A modification of the benzodiazepine structure is by the annelation of an additional ring system. For example, triazolam and midazolam, which are highly active substances result from the 1,2-annelation of triazole or imidazole (Fig 3).

The prolonged use of benzodiazepines is associated with the development of amnesia, tolerance and dependence (physical and psychological), and withdrawal problems. Withdrawal syndrome, on the other hand, is described as having rebound insomnia with the association of minor physical symptoms in addition to the symptoms specific to benzodiazepine withdrawal (13,14). Minor physical symptoms are tachycardia, tremor, perspiration, dizziness, palpitations, muscle tension or headache, and gastrointestinal symptoms such as nausea and vomiting. Symptoms specific to benzodiazepine withdrawal include changes of taste and smell, impaired vision and hearing, impaired perception of motion, de-personalization, de-realisation, paresthesia, loss of appetite or loss of weight and muscle spasm. In patients with pulmonary disease, all benzodiazepines...
can result in respiratory depression and the sleep-inducing efficacy may be lost with prolonged use (13, 14).

**Newer benzodiazepine-like agents**
Zolpidem and zaleplon (Fig 4) act as agonists at GABA receptors similar to classic benzodiazepines and can be used for chronic and transient insomnia. These benzodiazepine-like agents are able to cause shortened sleep latency and might lead to antegrade amnesia or idiosyncratic daytime sleepiness, and they don’t block withdrawal from benzodiazepines (13).

**Ethanol**
The most widely self-used hypnotic drug is ethanol. GABA receptors are important in mediating the CNS effects of ethanol in addition to voltage-gated calcium channels and ligand-gated ion channels. Chronic use of ethanol can lead to tolerance and dependence. It can reduce the efficiency and quality of sleep and increases the risk of severe daytime sleepiness and lowers daytime alertness.

**Sedating anti-histamines**
Sedating anti-histamines, more often diphenhydramine, are one of over-the-counter sleeping pills. They block H1 receptors and can result in anticholinergic effects that may affect driving performance, daytime sleepiness, cognitive and psychomotor impairment; tolerance might be a result of these agents. Moreover, the evidence for their efficacy and safety is very limited and they are not recommended for use in the elderly (13, 15).

**Exogenous melatonin**
This is an over-the-counter medication that is however not recommended in the treatment of chronic insomnia because of the lack of efficacy and safety data. Melatonin (Fig 5) is an endogenous hormone secreted by the pineal gland and is linked to the sleep cycle. It is not effective in the management of most primary sleep disorders with short term use. Trials evaluated the efficacy of melatonin as a chronobiotic (phase-shifting agent) rather than as a hypnotic. Headaches, dizziness, nausea, and drowsiness are the most common adverse effects (16, 17).

**Chloral hydrate and barbiturates**
Although FDA approved for use in treating insomnia, chloral hydrate and barbiturates are not generally recommended because of their likelihood of tolerance and dependence, adverse effects, low therapeutic index and loss of effects with chronic use (13, 17).

**Antidepressants**
Tricyclic antidepressants are mainly used for patients with chronic insomnia with associated symptoms of depression. Their limitations are overdose hazard and daytime hangover, and anti-cholinergic effects such as dry mouth, constipation, blurred vision, urinary retention, postural hypotension and erectile dysfunction. Sedating tricyclic antidepressants include amitriptyline, imipramine and nortriptyline.

**Herbal remedies**
A study published in Psychopharmacology in 2005 found that sleep-disturbed rats treated with 300 mg kava kava extract experienced a significant shortening in the sleep latency cycle. Although further human trials are required, researchers noted that kava...
Kava possesses sleep-quality enhancement effects. The University of Maryland Medical Center recommends taking 100-250 mg of standardized kava extract up to three times per day as needed. Another herbal remedy is chamomile. Valerian is another herb widely used as a sleep aid. The University of Maryland Medical Center recommends taking 200-400 mg of valerian standardized extract before bed to promote sleep.

**New approaches in treating insomnia**

Due to limitations of current treatments of insomnia, novel hypnotic drugs with different mechanisms of action and different targets for promoting sleep have been developed; some of these are currently in phase II/III clinical trials. Of the therapeutic agents listed in Table 1, gaboxadol, indiplon, almorexant, agomelatine and esmirtazapine are discussed in the following section.

**Gaboxadol**

Gaboxadol (Fig 5A) is a selective extrasympathetic GABA-A receptor agonist (18). Its functional activity is highest for δ-containing GABA-A receptors which exist mainly extrasympaptically and are localized in the thalamus, cerebellum, dentate gyrus and cortex. They are insensitive to traditional benzodiazepine (e.g triazolam) and non-benzodiazepine (e.g zolpidem) hypnotics. Gaboxadol improves sleep quality and positively affects daytime performance in primary insomniacs (1). When 15 mg of gaboxadol was used in adult patients, it decreased the amount of time spent in stage 1 sleep, had no significant effect on stage 2 sleep, and increased the amount of time spent in stages 3 and 4 sleep (19) and is generally well tolerated. The most common drug-related adverse experiences are dizziness, nausea, fatigue and vomiting. The pharmacokinetic parameters for gaboxadol showed that the mean $t_{1/2}$ was 1.7 h, $t_{\text{max}}$...
was 2 h, AUC$_{0-\infty}$ was 430 ng·h·ml$^{-1}$ and $C_{\text{max}}$ was 139 ng·ml$^{-1}$. The most notable difference in pharmacokinetics was the slightly shorter apparent terminal $t_{1/2}$ for elderly women compared to men. Regarding the renal excretion of gaboxadol, studies showed that an average of 58% of gaboxadol was recovered intact in the urine and the rest as glucuronide conjugate. The major metabolite excreted in human urine was gaboxadol-O-glucuronide (20, 21).

**Indiplon**

Indiplon (Fig 5B) is a pyrazolopyrimidine compound (22); it is an agonist for benzodiazepine receptors and has high selectivity and affinity for the $\alpha_1$-subtype of the GABA-A receptor complex. It improves sleep onset, sleep duration and maintenance, and overall sleep quality in primary insomnia. Studies have shown that this improvement in sleep was sustained across all 3 months of study treatment with no change in response with time. Indiplon also improves daytime functioning and quality of life in patients with primary insomnia symptoms (23, 24).

There are two formulations for indiplon; Indiplon-IR (immediate release), which was developed for difficulties in sleep onset, and indiplon-MR (modified release), which was intended for sleep maintenance insomnia. Adverse effects include upper respiratory infection, amnesia, dizziness, headache and somnolence.

When compared with benzodiazepines, discontinuation of indiplon was not associated with any increase in benzodiazepine-like withdrawal symptoms (23, 24). For indiplon, healthy young males have shown $C_{\text{max}}$ at 0.73h with elimination $t_{1/2}$ of 1.97h, while females have reached $C_{\text{max}}$ at 0.82h with elimination $t_{1/2}$ of 1.71. In the elderly population, impaired renal and hepatic functions can result in a 3-fold increase in plasma concentrations of indiplon and a doubling of $t_{1/2}$ compared to the values seen in younger adults.

Two major metabolites, N-desmethyl-indiplon and N-deacetyl-indiplon are observed. N-desacetyl-indiplon is formed by the cytochrome P450 CYP3A4 and CYP1A2 metabolic pathways, while N-deacetyl-indiplon is formed by microsomal carboxylesterases (25).

**Almorexant**

A tetrahydroisoquinoline derivative (Fig 5C), Almorexant is an orally potent dual (OX1R/OX2R) orexin receptor antagonist for the treatment of primary insomnia (26, 27). Orexin (or hypocretin) system exhibits a key role in the physiological and emotional responses that are associated with wakefulness such as stress processing, appetite and energy expenditure (28).

Orexins originate from a group of neurons in the lateral hypothalamus projecting to many of the ascending excitatory pathways. Orexinergic neurons are active during periods of wake and inactive during sleep; antagonising orexin activity by almorexant has a sleep-promoting effect.

Almorexant can promote REM and NREM sleep and decreases alertness (1, 27). Somnolence, fatigue, headache and nausea are reported as adverse effects. Muscular weakness was reported only with the highest almorexant dose (29). There were no significant effects on memory, motor performance, mood, calmness, subjective internal and external perception, and feeling high (29-30).

Almorexant is rapidly absorbed and distributed and has no tendency to accumulate with dose repetition. Almorexant has a median time to the $C_{\text{max}}$ of 1.5h and a quick disposition with a distribution $t_{1/2}$ of 1.6h. In addition, it has a rapidly decreasing concentration to approximately 20% of the $C_{\text{max}}$ over 8h and a terminal $t_{1/2}$ of 32h. After rapid absorption, almorexant is metabolised extensively, and the predominant route of elimination in humans is excretion of metabolites in faeces (26).

**Agomelatine**

Also known as S20098 this is a napthalenic compound with structural similarities to melatonin (2). The bioavailability of agomelatine is higher in women compared to men and it is increased with oral contraceptive intake and decreased with smoking (31, 32). Agomelatine (Fig 5D) is a melatonergic
agonist that acts on MT1/MT2 melatonergic receptors suppressing cAMP formation. Also, it acts as a complementary 5-HT2C antagonist and it enhances slow wave sleep without affecting REM sleep and can be used to treat depression (1).

The most common adverse effects are headaches, mild sedation and fatigue, dizziness and reversible elevations in serum alanine and/or aspartate transaminases. As a result, liver function tests should be performed at the onset of treatment, and then periodically at 6, 12 and 26 weeks. Hepatic impairment is a contraindication. Unlike older agents, agomelatine does not cause any withdrawal symptoms when discontinued. Agomelatine's therapeutic doses range between 25-50 mg/day (33, 34). It is absorbed rapidly from the gastrointestinal tract and transported immediately to the liver where it is metabolized by CYP1A1, CYP1A2 and CYP2C9 isoenzymes.

Four metabolites of agomelatine have been identified. These metabolites are excreted through urine and faeces, and only low levels of unchanged agomelatine are excreted. It has a short t½ of about 2h. Its dissociation constant for MT1/MT2 melatonin receptors is 10 nM which is similar to that of melatonin (33, 34).

**Esmirtazapine**

An antagonist on the presynaptic α2 adrenergic receptors as well as postsynaptic 5HT2 and H1 receptors, esmirtazapine (Fig 5E) has higher affinity to 5-HT2 receptors and low affinity to 5-HT3 receptors when compared with mirtazapine and R-mirtazapine. Racemic mirtazapine is used for the treatment of major depressive disorder. Esmirtazapine is in phase III clinical development for the treatment of primary insomnia and hot flushes. Doses when used for insomnia are lower than those prescribed for depression. The effective sleep promoting doses of esmirtazapine range between 1.5-4.5 mg (36).

Somnolence and fatigue are the most frequently reported adverse events. Esmirtazapine has a long t½ of 20h which raises the issue of residual daytime drowsiness and driving impairment. Studies support the notion that dose effects of esmirtazapine on driving are related to the drug's concentration in plasma. Esmirtazapine is metabolized through cytochrome P450 CYP2D6 in the liver by demethylation and hydroxylation and formation of S(+)-N-desmethylmirtazapine and S(+)-8 hydroxymirtazapine, followed by glucuronide conjugation. Its clearance in poor metabolisers is twice lower when compared to extensive metabolisers (36).

**Conclusion**

Using herbals and natural drugs to treat insomnia is rarely effective. In addition, the side effects of the current medications for insomnia necessitate the de-
velopment of new agents. Novel drugs including gaboxadol, indiplon, almorexant, agomelatine, and esmirtazapine have reached phase III clinical trials and some are awaiting approval; these exhibit better safety profiles and lesser side effects and withdrawal symptoms. They have variable pharmacokinetic properties as some of them have short $t_{1/2}$ and some have long $t_{1/2}$. They act on different receptors and by different mechanisms and some of them can be also used in other depressive disorders.

References

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Household cleaning products may contain toxic substances linked to health problems such as asthma, allergic reactions, and cancer, according to a report by the US Environmental Working Group (EWG).

They rated more than 2,000 household cleaners - from laundry soaps and stain removers to bathroom cleaners and floor care products. Products are graded A to F based on the safety of the ingredients and how well the maker discloses those ingredients.

One industry trade group disputes the findings though, saying the report doesn't make the grade.

According to the EWG report, more than half the products evaluated contain ingredients known to harm the lungs. In other cases, it was difficult to determine what was in the product because of incomplete labeling.

Ninety-three percent [of the products] provided ingredient lists that were incomplete or not specific enough. Few 'green' brands were still reticent about their ingredients.

Cleaning products are largely unregulated. Some cleaning products did get high marks. Among the many products that received an A rating:

- Whole Foods Market green MISSION Organic Answers to MCQs on back page

Is there a problem?

A 56 year old patient was prescribed the drug given in the prescription for hypertension. Is there any major error?

KLM HOSPITAL

Patient Name: Mr. Ahmad Ali Age: 56 years
Address: Street No. 7
Rx
Nifedipine 5mg tablet
One tablet three times a day
Send one pack
Dr. MXD
Signature Date: 15/06/13

Immediate release nifedipine is not recommended for hypertension. Modified release nifedipine is recommended for treatment of hypertension.

Example: Adalat LA® (nifedipine) 20-30mg once daily, maximum dose 90mg once daily. (Source: British National Formulary)

TEST YOUR KNOWLEDGE

1) Which of the following is a sleep promoting neurotransmitter?
   a) serotonin
   b) galanine
   c) noradrenaline
   d) dopamine
   e) histamine

2) Which of the following develops with prolonged use of benzodiazepines?
   a) amnesia
   b) tolerance
   c) physical dependence
   d) psychological dependence
   e) all of the above

3) Which of the following is a GABA-A BZ site modulator awaiting approval for indication in sleep disorders?
   a) agomelatine
   b) esmirtazapine
   c) gaboxadol
   d) indiplon
   e) almorexant

TOPICAL ISSUES AND CONTROVERSIES

Toxins in cleaning products?
All-Purpose Spray Cleaner & Degreaser, Lemon Zest for general cleaning
- Arm & Hammer Baking Soda for general cleaning
- Seventh Generation National Tub & Tile Cleaner, Emerald Cypress & Fir
- Green Shield Organic toilet bowl cleaner
- The Honest Co. auto dishwasher gel, free & clear

EWG Guide: Details
EWG scientists compared the ingredients listed on the labels of cleaning products and manufacturers' web sites with information from toxicity databases from government, industry, and academic sources. They looked at medical literature on health and environmental problems linked with cleaning products.

Among the key findings, according to EWG:
- About 53% of the products had ingredients known to harm the lungs. Examples are benzalkonium chloride, found in antibacterial cleaners, and chlorine bleach.
- About 22% had chemicals linked with asthma in previously healthy people.
- Some products use formaldehyde, a known human carcinogen, as a preservative, or it is released by other preservatives in the products.
- The chemical 1,4-dioxane, suspected of being a human carcinogen, is a common contaminant of detergent chemicals.
- Chloroform, also a suspected carcinogen, can escape in fumes released by products containing chlorine bleach.
- Sodium borate, sometimes called borax or boric acid, is added to many products. It can be a hormone disrupter.

EWG scientists suggest entirely avoiding some products because of ingredients. These include air fresheners, antibacterial products, fabric softeners, and caustic drain cleaners and oven cleaners.

EWG said even some "green brands" could do better on disclosing ingredients. Among them: Earth Friendly Products and BabyGanics. A spokeswoman for BabyGanics, said it was unfortunate that the EWG deemed their descriptions inadequate. She noted “one problem is a lack of uniform industry standards. All BabyGanics products contain ingredient statements, including our household, hand hygiene, diapering, skin care, sun care, and oral care solutions. The household product category remains the only one that still does not have a uniform set of industry standards."

It is a fact that anything can be safe or unsafe - it all depends on the amount. Manufacturers work to ensure that they use levels of ingredients that are 'just right' - in that they provide a benefit in the products, but at the same time are safe. One option is to make your own cleaning products from white vinegar and water.

Drug safety standards: need for transparency
Historically, the evaluation of harmful effects resulting from prescription drug use has been considered less important than demonstrating drug efficacy, yet the harms caused by specific adverse drug reactions are a major, and avoidable, contributor to hospitalizations and deaths.

There are many reasons (both scientific and social) why reliable data on harmful effects may only emerge well after drug approval and marketing. Drugs approved under a rapid regulatory review process may be more likely to show problems with safety post-marketing than drugs that go through a slower evaluation process. And debates continue about the best ways to meaningfully synthesize and interpret data on the possible harmful effects of drugs—for example, how passive surveillance systems (spontaneous reports of suspected adverse reactions) should be improved, whether new drugs should go through a phased launch process with enhanced safety evaluations, and whether risk mitiga-
Eyes grown from stem cells

With the proper culture conditions, mouse embryonic stem (ES) cells can spontaneously form the rudiments of a retina. The results, published in *Nature*, could help researchers answer some outstanding questions about eye development and dysfunction, and hold promise for the development of retinal tissues for transplantation.

For the last decade, developmental biologist Yoshiki Sasai at the RIKEN Center for Developmental Biology in Japan and his colleagues have worked to differentiate ES cells into various cells of the nervous system, including cerebral cortex neurons and retinal cells. They were interested in more than just generating different nerve cells and wanted to learn how those cells come together to form entire tissues and already showing signs of setting high standards in some areas.

Studies conducted solely by industry will not be eligible to qualify for ENCEPP approval; studies must be publicly registered before collection of data, and protocols and datasets must be released (with some restrictions relating to data privacy) in a timely way after completion. Critically, ENCEPP can still potentially approve studies funded by the pharmaceutical industry, with involvement of industry partners in design and analysis, providing the study's lead investigator is based within an ENCEPP-approved center. More worryingly, the code allows for industry sponsors to retain control of datasets; this, and other provisions, may enable conflicts of interest to creep in during study design or data analysis.

Clearly, for post-approval safety studies, one size will not fit all. Conduct and reporting are unlikely to be standardisable in the same way as has been possible for randomized trials, in which there is agreement on what information needs to be registered about the study and when, and specific standards for the reporting of studies are widely accepted. The ENCEPP guidance avoids normative statements about study design, instead preferring to highlight the methodological challenges and multiple sources of bias that plague analysis and interpretation of data. However, these challenges should not discourage investigators, regulators, and patients from demanding a higher safety standard for approved drugs.

Higher standards will require both greater transparency- in revealing what studies are being conducted and what data that have been generated- and greater willingness of funders to support new studies specifically addressing drug safety.

organs in developing embryos. Starting with the culture conditions they had established for retinal differentiation, the researchers added matrix proteins that they hoped would encourage the formation of the more rigid retinal epithelial structures. They then seeded the culture with mouse ES cells.

Within a week, the cells formed small vesicles and differentiated into two different tissue types: Cells on one side of the vesicles formed the mechanically rigid pigment epithelium, while cells on the other side differentiated into a more flexible tissue that folded inward in the shape of an embryonic optic cup— the retina's precursor.

The biggest surprise was that we observed the formation of the very real optic cup structure that mimicked both the shape and tissue composition and popped out from the [ES cell] aggregate.

The generation of retinal tissue from ES cells is an exciting advance that may lead to regenerative medicine applications. While doctors are not about to start transplanting these synthetic retinas, ES cells cultured under the proper conditions could yield certain cells that may prove therapeutically valuable.

The system might help answer how ES cells self-organize into the complex retinal tissues. While the retinal structures cultured in this study only developed into neonatal mouse retinas, which still lack photoreceptor cells, it will likely just take a few tweaks to the culture conditions to coax those structures into mature retinas, allowing researchers to examine the entire process.

Furthermore, if researchers can replicate the results using human induced pluripotent stem (iPS) cells, it could shed light on retinal dysfunction. By creating iPS cells from patients with [visual disorders] and then making synthetic retinas from such iPS cells, we could potentially study the disease process caused by particular genetic defects.

Source: http://www.the-scientist.com/news/display/58105/

**NEWS from the FDA**

Using innovative technologies and other conditions of safe use to expand which drug products can be considered nonprescription

FDA held a public hearing, in March 2012, to obtain input on a potential new paradigm under which FDA would approve certain drugs that would otherwise require a prescription for nonprescription use under conditions of safe use specific to the drug product.

**A. Prescription and nonprescription drugs**

Prescription drugs are dispensed upon receipt of a prescription from a practitioner licensed by law to administer the drug (which may include health care professionals such as physicians, nurse practitioners, physician's assistants, and others whom we will refer to here as practitioners or prescribers). In many instances, under the current regulatory system, a patient has to obtain at least the initial prescription, and in some cases, prescription refills, from a practitioner through an in person interaction. Obtaining a refill for other prescription drugs involves at least a telephone call or other communication with the practitioner. In contrast, nonprescription drugs (sometimes referred to as over-the-counter or OTC products) can be purchased by consumers in pharmacies, supermarkets, and other retail establishments without the need for a prescription.

Currently, consumers can purchase nonprescription drugs from a retailer for diseases or conditions that do not meet the statutory criteria for prescription products and that are safe and effective for use in self-medication as directed in the labeling. Generally, OTC products: (1), Are available to treat diseases or conditions that can be self-diagnosed without a prior interaction with a practitioner (2), are not associated with toxici-
ties that require an evaluation of the benefits and risks by a practitioner and (3), do not require a practitioner’s input for use.

**B. Under-treatment of diseases and other effects on the health care system**

Under-treatment of many common diseases or conditions in the US is a well-recognized public health problem. Increasing the number of people who are able to obtain for the first time and those who continue on necessary drug therapy could provide improved health outcomes.

The requirement to obtain a prescription for appropriate medication (and to make one or more visits to a practitioner) may contribute to undertreatment of certain common medical conditions including hyperlipidemia (high cholesterol), hypertension (high blood pressure), migraine headaches, and asthma. For instance, some consumers do not seek necessary medical care, which may include prescription drug therapy, because of the cost and time required to visit a health care practitioner for an initial diagnosis and an initial prescription. Some patients who obtain an initial prescription do not continue on necessary medication because they would need to make additional visits to a health care practitioner for a prescription refill after any refills authorized by the initial prescription have been used or the time during which they can be filled has expired. Some prescription medications require routine monitoring through the prescribing practitioner such as blood tests to assist in the diagnosis of a condition, or to determine whether or how well the medication is working, or to adjust the dose.

In addition to improved health outcomes for consumers staying on their medications, the time and attention that physicians and other health care providers expend on routine tasks related to prescription refills reduces the time that they are available to attend to more seriously ill patients. Eliminating or reducing the number of routine visits could free up prescribers to spend time with more seriously ill patients, reduce the burdens on the already overburdened health care system, and reduce health care costs.

FDA is aware that industry is developing new technologies that consumers could use to self-screen for a particular disease or condition and determine whether a particular medication is appropriate for them. For example, kiosks or other technological aids in pharmacies or on the Internet could lead consumers through an algorithm for a particular drug product.

Some drug products that would otherwise require a prescription could be approved as nonprescription drug products with some type of pharmacist intervention as their condition of safe use. For example, some diseases or conditions might require confirmation of a diagnosis or routine monitoring using a diagnostic test (e.g., a blood test for cholesterol levels or liver function) that could be available in a pharmacy. A pharmacist, or consumer, could then use the results to determine whether use of a certain drug product is appropriate. Other potential roles for the pharmacist include assessing whether the consumer has any conditions or other risk factors that would indicate that the drug should not be used, or assisting the consumer in choosing between various drug products. For drugs that require use of a diagnostic test, creating a pathway for nonprescription use may result in the development by industry of diagnostics suitable for use by the patient or a pharmacy professional.

FDA is also considering whether the same drug product could be simultaneously available as both a prescription and nonprescription product with conditions of safe use. Dual availability could help ensure greater access to needed medications by making obtaining them more flexible. Consumers could choose to continue seeing their health care practitioner to diagnose diseases or conditions and obtain prescriptions, and when their local retail establishment is not equipped to offer the nonprescription product with conditions of safe use. Other consumers could take advantage of the ability to obtain nonprescription products with conditions of safe use where they are available.

*Source: https://www.federalregister.gov/articles/2012/02/28/2012-4597/using-innovative-technologies-and-other-conditions-of-safe-use-to-expand-which-drug-products-can-be*
FDA issues draft guidance on biosimilar product development

In February 2012 the US FDA issued three draft guidance documents on biosimilar product development to assist industry in developing such products in the US.

These draft documents are designed to help industry develop biosimilar versions of currently approved biological products, which can enhance competition and may lead to better patient access and lower cost to consumers.

The Patient Protection and Affordable Care Act, signed into law by President Obama on March 23, 2010, amended the Public Health Service Act to create an abbreviated approval pathway for biological products that are demonstrated to be highly similar (biosimilar) to or interchangeable with an FDA-licensed biological product.

Biological products are therapies used to treat diseases and health conditions. They include a wide variety of products including vaccines, blood and blood components, gene therapies, tissues and proteins. Unlike most prescription drugs made through chemical processes, biological products are made from human and/or animal materials.

A biosimilar is a biological product that is highly similar to an already approved biological product, notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biosimilar and the approved biological product in terms of the safety, purity, and potency.

Through this new approval pathway, biological products are approved based on demonstrating they are biosimilar to, or interchangeable with, a biological product that is already approved by the FDA, which is called a reference product.

The following three guidance documents provide the FDA’s current thinking on key scientific and regulatory factors involved in submitting applications for biosimilar products to the agency. FDA is seeking public comment on these draft guidance documents:

Scientific considerations in demonstrating biosimilarity to a reference product
The draft guidance is intended to assist companies in demonstrating that a proposed therapeutic protein product is biosimilar to a reference product for the purpose of submitting an application to the FDA. This draft guidance describes a risk-based “totality-of-the-evidence” approach that the FDA intends to use to evaluate the data and information submitted in support of a determination of biosimilarity of the proposed product to the reference product. As outlined in the draft guidance, FDA recommends a stepwise approach in the development of biosimilar products.

Quality considerations in demonstrating biosimilarity to a reference protein product
The draft guidance provides an overview of analytical factors to consider when assessing biosimilarity between a proposed therapeutic protein product and a reference product for the purpose of submitting the appropriate application. This includes the importance of extensive analytical, physico-chemical and biological characterization in demonstrating that the proposed biosimilar product is highly similar to the reference product notwithstanding minor differences in clinically inactive components.

Biosimilars: questions and answers regarding implementation of the biologics price competition and innovation act of 2009
The draft guidance provides answers to common questions from people interested in developing biosimilar products. The question and answer format addresses questions that may arise in the early stages of product development, such as how to request meetings with the FDA, addressing differences in formulation from the reference product, how to request exclusivity, and other topics.

Adapted from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm291232.htm
**New Pharmaceutical products approved from January to May 2013**

- Abilify Oral Solution. 1mg/ml; Aripiprazole-1mg; Bristol Myers Squibb Co. U.S.A.
- Abraxane for Injectable Suspension 100mg (albumin-bound); Paclitaxel-100mg, Human Albumin-900mg; Abraxis Bioscience LLC - U.S.A.
- Asitalox Tablets 10, 20mg: Escitalopram-10, 20mg; Aurobindo Pharma Ltd - India
- Aurotaz P 4.5g Injection; Piperacillin -4g, Tazobactam -0.5g; Aurobindo Pharma Ltd.- India
- Azcom Aqueous Nasal Spray 0.05%; Mometasone Furoate-50µg; Middle East Pharma Ind. Co. Ltd. - K.S.A.
- Calciferol Biotika Forte Solution for Infusion 300,000 IU (7.5mg);Ergocalciferolum-300,000IU; Biotika Bohemia, spol.r.a
- Danzen Tablets 5mg; Serratiopeptidase 5mg; APM Co. Ltd.- Jordan
- Elaprase Solution for IV Infusion 6mg/3ml; Idursulfase 6mg/3ml; Shire Human Genetic Therapies Inc- U.S.A.
- Eliquis Tablets 2.5mg; Apixaban-2.5mg; Bristol Myers Squibb/Pfizer EEIG- U.K.
- Floratil Capsules 250mg; Saccharomyces boulardii-250mg; Merck KgaA- Germany
- Floratil Powder for Oral suspension. Sachet 250mg; Saccharomyces boulardii 250mg; Merck KgaA- Germany
- Gaviscon Advance Peppermint Flavour Oral Suspension; Sodium Alginate-1000mg, Potassium hydrogen carbonate 200mg; Reckitt Benkiser- U.K.
- Gemcitabine Ebewe Concentrate for solution for Infusion 1000mg/25ml; Gemcitabine-1000mg; Ebewe Pharma Ges m.b.H NFGKG- Austria
- Gemcitabine Ebewe Concentrate for solution for Infusion 2000mg/50ml; Gemcitabine-2000mg; Ebewe Pharma Ges m.b.H NFGKG- Austria
- Gemcitabine Ebewe Concentrate for solution for infusion 200mg/5ml; Gemcitabine-200mg; Ebewe Pharma Ges m.b.H Nfg KG
- GETZ Freeze Dried for Injection 200mg, 1g; Gemcitabine 200mg, 1g; Lab Richmond S.A.C.I.F- Argentina
- Glitra Tablets 1,2,4mg; Glimepiride 1,2,4mg; JPM- Jordan
- Glypride Tablets 1,2,3,4mg; Glimepiride-1,2,3,4mgJulphar; Gulf Pharmaceutical Industries (Julphar) U.A.E.
- Hibiott Tablets 1g; Amoxicillin Anhydrous-875mg, Clavulanic Acid-125mg; Amoun Pharmaceutical company - Egypt
- Kardam Tablets 5mg; Amlodipine-5mg; Aurobindo Pharma Ltd - India
- Klar Tablets 250,500mg; Clarithromycin 250,500mg; Aurobindo Pharma Ltd.- India
- Lanzopral Capsules 15mg; Lanzoprazole 15mg; Ram pharm Ind. Co. Ltd. - Jordan
- Levox Infusion IV; Levofloxacin Hemihydrate 500mg; Claris Lifesciences Ltd.- India
- Loratadina Korhispana 10mg Tablets; Loratadine-10mg; Lab. Korhispana- Spain
- Lorinase Tablets; Loratadine 5mg Pseudoephedrine 120mg; Spimaco - K.S.A.
- Lorvas SR Tablets 1.5mg; Indapamide-1.5mg; Torrent Pharma Ltd.- India
- Meropenem powder for Solution for Injection/Infusion 500mg,1g; Meropenem 500mg,1g; Hospira U.K. Ltd. – U.K.
- MF-Day Tablets 500,850mg; Metformin-500,850mg; Aurobindo Pharma Ltd.- India
- Modiodal Tablets 100,500mg; Modafinil-100,500mg; Cephalon France- France
- Mofetab Tablets 500mg; Mycophenolate Mofetil 500mg; Tabuk Pharmaceutical company- K.S.A.
- Ozurdex Intravitreal Implant in applicator 700mcg; Dexamethasone 700mcg; Allergan Pharmaceuticals - Ireland
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