Epilepsy is a brain disorder that has been affecting people since the beginning of recorded history. According to the WHO it currently afflicts 50 million people worldwide, almost 80% of them in developing regions. The economic burden of epilepsy accounts for about 0.5% of the global burden of disease. The total cost per epilepsy case is estimated at about US$ 350 per year. Epilepsy is defined by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) as “an enduring predisposition of the brain to generate epileptic seizures, with neurobiological, cognitive, psychological, and social consequences” and seizures are defined as “a transient occurrence of signs and/or symptoms due to abnormal excessive and synchronous neuronal activity in the brain”.

Pathophysiology

Abnormal electrical activity
A seizure, which is the main manifestation of epilepsy, results from an excessive spontaneous discharge of neurons in the cortical or subcortical regions of the brain. The burst of action potentials usually coincides with a paroxysmal depolarization shift during which a sustained plateau neuronal depolarization occurs because of the binding of the main excitatory neurotransmitter glutamate to its receptors, mainly NMDA receptors, causing an influx of calcium, which then leads to the opening of voltage-gated sodium channels leading to an influx of sodium. The depolarization is then followed by a rapid repolarization and finally hyperpolarization, which is mediated by the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) resulting in either a chloride influx or potassium efflux, depending on the cell type.

The imbalance between excitatory and inhibitory neurotransmitters, in the form of increased glutamate or decreased GABA, may explain the hyperexcitability of the neurons in the focus.

Alterations in ion-channels
Functional or structural alterations in the post-synaptic membrane involving the number, type, or distribution of ion-channels can increase the excitability of neurons. For example, genetic changes in the types of subunits α and β of sodium channels influence the shape of the action potential leading to a number of epilepsy syndromes, such as Dravet syndrome and severe myoclonic epilepsy in infants. Another important channel is the T-type calcium channel that if expressed in high density may lead to increased electrical bursts because it has a lower threshold than other subtypes of calcium channels or sodium channels. Hence, a minimal depolarization can lead to the opening of these channels and further depolarization, ultimately leading to a low threshold spike and subsequently excessive firing of action potentials. This channelpathy is of importance in the pathophysiology of absence seizures.
**Alterations in receptors**

Other mechanisms that may explain the loss of normal balance in excitation and inhibition include biochemical modification of glutamate or GABA receptors. Glutamate has three subtypes of receptors, two of which are coupled to ion channels: the N-methyl-D-aspartate (NMDA) and non-NMDA receptors. The activation of the NMDA receptors leads to slow long-lasting excitatory post-synaptic potentials (EPSP), while the activation of Non-NMDA receptors, which include the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors, causes fast brief EPSP. An abnormal structure of NMDA receptor such as, the lethal global elimination of the NMDA receptor subunit NR1 increases seizure susceptibility.

**Alterations in extracellular ions and neurotransmitters**

Epileptogenesis is also explained by alterations in the concentrations of extracellular ions, and changes in the uptake and metabolism of neurotransmitters in glial cells. These cells play an important role in the maintenance of extracellular levels of ions and neurotransmitters, especially the restoration of potassium homeostasis after neuronal activity.

**Spreading and amplification**

The hyper-synchronisation of excessive firing of action potential is a hallmark in the pathophysiology of epilepsy. The amplification and spread of activity among surrounding neurons occurs via synaptic transmission, gap junctions, ephaptic interactions, or changes in extracellular ion concentrations.

In synaptic interaction, a transmitter released by presynaptic terminals activates postsynaptic cells resulting in the generation of inward or outward currents, which depolarise or hyperpolarise the postsynaptic cell.

Another way of communication among adjacent neurons is electrically via gap junctions. This occurs when there is a direct flow of ions from one neuron to another in direct contact. Ephaptic interaction is minimal yet more widely spread and of great influence if the neuronal network is already synchronised by other means. This ephaptic, or electrical field, is an extracellular current produced by electrical activity of neurons affecting the electrical properties of the network. Lastly, pronounced changes in the extracellular concentration of ions in one neuron might diffuse to a neighboring neuron resulting in its excitation.

Propagation of the seizure depends on the degree of activation and recruitment of the surrounding neurons. The neuronal discharge can either spread locally, which leads to a focal seizure, or widely, leading to generalised seizures.

**Treatments**

The current management of epilepsy aims for three main outcomes; to control seizures (seizure-free state), minimize treatment side effects, and maintain or improve patient’s quality of life.

**Membrane stabilisation**

Membrane stabilizers include sodium channel blockers that work on reducing neuronal excitability by suppressing the repetitive excessive firing of action potential and preventing depolarization of nerve terminals and consequently the release of glutamate. Blockage of voltage-gated sodium channel is the primary action of phenytoin, carbamazepine, lamotrigine, and topiramate. Other membrane stabilisers are potassium channel activators that promote neuronal hyperpolarization. An example of this class is retigabine. Another drug that works on activating potassium channels is flupirtine which is still under development as an anti-convulsant. The blockage of T-type calcium channels is another
mechanism by which some AEDs work e.g., ethosuximide and zonisamide.

**GABA augmentation**

Many AEDs potentiate GABAergic inhibition, e.g., vigabatrin. This drug works by inhibiting GABA transaminase to increase the pool of extracellular GABA. Blocking the re-uptake of GABA release by tiagabine also leads to increased GABA-mediated inhibition. Other drugs work directly on GABA-A receptors as positive allosteric modulators. These inhibitory receptors contain binding sites for GABA, benzodiazepines, barbiturates and neurosteroids. Benzodiazepines, e.g., clonazepam, which increase GABA-A channel opening frequency, and barbiturates as phenobarbital, which prolong the channel opening time, are useful AEDs. Other AEDs that work as positive allosteric modulators for GABA-A receptors include ganaxolone and stiripentol.

**Neurotransmitters reduction**

Drugs like gabapentin and pregabalin inhibit neurotransmitter release by binding to the α2δ subunit of presynaptic N and P/Q type calcium channels, reducing the calcium influx that triggers neurotransmitters release. Another mechanism that ultimately leads to decreased neurotransmitter release is the binding and inhibition of synaptic vesicle protein, e.g. SV2A by levetiracetam, seletrace tam, and brivaracetam.

**Glutamate inhibition**

Glutamate is another therapeutic target for the treatment of epilepsy. NMDA receptors are blocked by felbamate and fluorofelbamate, while the AMPA receptor is antagonized by non-competitive blockers like talampanel. Moreover, topiramate selectively blocks excitatory synaptic transmission mediated by GluR5 kainate receptors as well as the AMPA receptor.

**Resistant epilepsy**

Resistance to anti-epileptic drugs is a serious clinical problem in the management of epilepsy. Approximately 30% of epilepsy cases are refractory to treatment despite several trials of different AEDs. Patients with drug-resistant epilepsy are more susceptible to premature death, injuries, psychosocial dysfunction, and reduced quality of life. Resistance is “the failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.”

**Predictors of resistance**

Several factors can predispose and predict resistant or refractory epilepsy. A study on newly diagnosed epilepsy patients concluded that high frequency of seizures before treatment and lack of response to the initial AED predispose a person to pharmacoresistance. Another predictor for resistance is the etiology of seizures; idiopathic seizures have better prognosis than symptomatic and cryptogenic seizures. Patients who suffer from focal seizures are at a higher risk of resistance than those with generalized ones. Early seizure onset, family history, abnormal EEG findings, structural brain abnormalities, occurrence of status epilepticus, and history of febrile seizures may also be factors that increase the probability of intractability.

**Hypotheses of resistance**

Based on several studies, currently two main hypotheses have been put forward to explain the mechanism of resistance. One theory is related to the drug transporter and known as the “transporter hypothesis”, while the other is related to the drug target and known as the “target hypothesis”. The transporter hypothesis suggests that resistance may be due to the over-expression of multidrug efflux transporters in the epileptogenic focus. These transporters are transmembrane proteins that pump substances and xenobiotic out of the cell against the concentration gradient.

An example of these is P-glycoprotein (P-gp) that is highly expressed in the capillary endothelial cells of the blood brain barrier. The excessive efflux of AEDs from extracellular space back to the capillary lumen results in reduced cerebral accumulation of the drug and its failure to reach the target.

Over-expression of P-gp in the hippocampus of drug resistant rats with temporal epilepsy was observed when given maximum tolerated doses of phenobarbital. Moreover, the administration of tariquidar, a selective P-gp inhibitor, along with the phenobarbital to phenobarbital-resistant rats restored the anticonvulsant effect of phenobarbital. P-gp is encoded by the ABCB1 gene; therefore polymorphism in this gene may be associated with different response to AEDs. However, other studies have failed to find any association between genetic polymorphism and the response to AEDs.
Target hypothesis postulates that alterations to one or more drug target reduce their sensitivity and subsequently the efficacy of AEDs in refractory epilepsy. These drug targets include voltage-gated ion channels, neurotransmitter receptors, and metabolic enzymes responsible for neurotransmitter uptake or release.

Several studies showed that there was a loss of use-dependent block of voltage-gated sodium channels by carbamazepine in patients who are resistant to this drug. It was also found that the fast recovery from inactivation was markedly slowed by carbamazepine in carbamazepine-responsive patients compared to those who are resistant. Similar results were also found with phenytoin but not lamotrigine.

Other studies have discussed the possible association between mutations in the SCN2A gene, which encodes the α2 subunit of the neuronal sodium channels, and resistance to AEDs.

GABA receptors, especially, the GABA-A receptor, might have a role in resistance. This receptor is assembled from seven subunits, α1β2γ2ε2δ2, being the most common assembly in brain regions. This assembly renders the receptor sensitive to benzodiazepine, hence modifications, such as the presence of α4 or α6, can make the receptor insensitive to benzodiazepine and possibly other AEDs.

Due to several unresolved issues, other possible hypotheses that might explain intractable epilepsy were developed: the network hypothesis, the genetic variant hypothesis, and the internist severity hypothesis. The new neural network hypothesis suggests that seizure-induced changes in the brain plasticity possibly due to uncontrolled epilepsy can lead to abnormal neuronal networks that hinder the effect of AEDs.

Another hypothesis proposes that resistance could be due to genetic variants of the proteins involved in the pharmacokinetics and pharmacodynamics of AEDs. Examples of mutations related to the dynamics of AEDs, are mutations in SCN1A and SCN2A genes that encode the α-subunits of sodium channels.

The association between the severity of epilepsy and resistance may also justify intractability. Several findings correlated the frequency of seizures with the prognosis of epilepsy; higher number of seizures in early stages of epilepsy is correlated with poorer outcome. Hence, the frequency of seizures is an easily quantifiable measurement of epilepsy severity. This hypothesis is criticized due to the lack of current knowledge regarding epilepsy severity and the clinical markers to determine it.

Developing tolerance to drugs after repeated administrations is a prominent pharmacological phenomenon, which can play a role in refractory epilepsy. The extent of the developed tolerance differs depending on the drug and the individual.

Tolerance to AEDs can be of two types: pharmacokinetic and pharmacodynamic. The kinetic or metabolic tolerance is due to the up regulation of the drug’s metabolic enzymes and can be overcome by increasing the dose. This tolerance is reversible by discontinuing the drug, whereas pharmacodynamic tolerance is related to the adaptation of the drug targets where there is a loss of sensitivity. This functional tolerance can lead to a complete loss of AED activity and cross-tolerance to other AEDs.

**Challenges in treatment of resistant epilepsy**

Several challenges have limited the management of drug-resistant epilepsy. Current AEDs have limited efficacy as they only work on preventing seizures rather than correcting the underlying epileptogenesis. Moreover, the side effects associated with AEDs can limit their long term use. Pharmacoresistant patients are more likely to be on more than one drug, therefore there is a higher incidence of side effects and drug-drug interactions between the AEDs or with other medications. The high cost of AEDs can also be a barrier to treatment success, especially in developing countries. All of these problems associated with the currently available AEDs can lead to non-compliance resulting in failure of therapy and breakthrough seizures.

Limitations in managing refractory epilepsy are also due to problems in drug development. The chance that a new drug completes the development process is only 10%; therefore the process is costly, risky, and expensive.

The availability of many AEDs in the market and the lack of understanding of the exact mechanism of resistance have pushed drug companies away from this direction.

During drug development, efficacy and safety are tested using animal models. These models have been criticized as the use of the current models will result in developing drugs with similar mechanisms and properties of the current AEDs and therefore have no role in the management of refractory epilepsy. More-
over, because resistance can be due to several different and not fully understood mechanisms, these few animal models are not enough to aid new drug development. For these reasons, the use of animal models that resemble resistance is very important, e.g., phenytoin-resistant kindled rats. A third challenge related to animal models is that even in vivo models are not enough to predict human response and tolerability to side effects.

Lastly, variability among patients can also explain therapy failure in some cases. Patients develop tolerance to AEDs differently, depending on the drug and genetic factors. Therefore, understanding pharmaco-genetic alterations that can affect the response, tolerability, and metabolism of AEDs is an important approach to overcome epilepsy resistance.

**Current and future managements of refractory epilepsy**

**Anti-epileptic drugs**

Current approaches to manage intractable epilepsy can be pharmacological by using AEDs or non-pharmacological by surgical interventions or brain stimulation. Once intractable epilepsy is appropriately diagnosed, a drug regimen is chosen based on the seizure type, frequency, and previous response to AEDs, to achieve the best possible seizure control.

Combination therapy is widely used for the management of drug-resistant epilepsy. A rational regimen involves establishing optimal dosage of an agent and then adding another AED with a different mechanism of action. A third agent can be added if there is sub-optimal control of seizures.

Although there is no clear-cut evidence for an optimal combination, the use of valproic acid with lamotrigine produced synergistic beneficial effects in refractory epilepsy. However, this combination is clinically challenging due to pharmacokinetic interactions requiring lowering the dose of lamotrigine. Other suggested combinations include the use of carbamazepine with valproic acid, and lamotrigine with topiramate.

**Surgery**

Surgical treatment has also been utilized to manage drug-resistant epilepsy. Candidates of surgical interventions include those who have failed to respond to at least two appropriate AED trials and those with significant disabling epilepsy. The epileptogenic focus should be well localized and the region should be functionally silent so that its surgical removal does not result in significant cognitive or neurological deficit.

Patients with generalized epilepsy or multifocal onset epilepsy are not considered appropriate candidates for surgical treatment. Examples of epilepsy cases that are likely to benefit from surgical interventions include mesial temporal lobe epilepsy and focal epilepsy with underlying lesional abnormalities, such as tumors or cortical dysplasia. Lesionectomy and temporal lobe resection are the most performed surgeries. Based on a trial in patients with temporal lobe epilepsy, temporal lobectomy was associated with higher seizure-free occurrence than medical treatment with AEDs.

**Neuro-stimulation**

Three systems have been developed and approved for the treatment of medically intractable epilepsy; vagus nerve stimulation, responsive neuro-stimulation, and stimulation to the anterior nuclei of the thalamus.

Vagus nerve stimulator (VNS) is a battery-powered device, like a pacemaker, that sends programmed electrical pulses to stimulate the left vagus nerve. This nerve is mostly composed of sensory afferent nerve fibers with cell bodies clustered in the ganglion in the brain and projected mainly towards nucleus tractus solitaries (NTS). The NTS then relays signals to different areas of the brain including the cortex, amygdala, thalamus, and locus ceruleus. Thus, the stimulation of the afferent fibers of this nerve can affect several cranial networks. Several theories are proposed to explain how VNS exerts an anti-epileptic effect.

Responsive neuro-stimulation (RNS) was approved by the FDA for the management of refractory epilepsy in 2013. Unlike VNS, the RNS system is a closed-loop feedback system as it records electrical changes to predict a seizure and terminates it with reversed current injection before it is clinically apparent. This
non-continuous stimulation is associated with fewer side effects. A randomized control trial on patients with medically intractable partial-onset epilepsy originating from one or two foci showed that responsive cortical stimulation with the RNS system was effective and safe over a mean follow up period of 5 years.33

Deep brain stimulation of the anterior thalamus has shown promising results. According to studies, lesions in the anterior thalamus were associated with reduced occurrence and frequency of induced seizures.34 This may be explained by the fact that the anterior thalamus receives electrical signals from the amygdala and hippocampus and then projects them as part of the limbic system. It might be involved in the amplification and synchronization of the electrical signals. Multiple studies proposed that bilateral stimulation of the anterior nuclei of the thalamus reduced seizures.35

Ketogenic diet
Ketogenic diet has demonstrated efficacy in some patients with refractory epilepsy. This diet is based on the consumption of low carbohydrates, high fat, and adequate amount of protein. This unbalanced diet will result in metabolic changes in the level of plasma ketones, glucose, insulin, and fatty acids. Because of the low intake of carbohydrates, the body will shift to starvation state, in which fatty acids are converted to ketones for energy.

A meta-analysis of 19 studies concluded that after six months of starting the diet, around 60% of children experienced greater than 50% seizure reduction with 30% having more than 90% reduction in seizure occurrence.36 Several theories have been proposed to clarify the mechanism by which this diet exerts its action. Studies have demonstrated that acetoacetate and acetone have anti-convulsant effects. Separately or collectively, the high fatty acids and ketone levels and low glucose level might be associated with an increased level of GABA, decreased reactive oxygen species, or reactivated potassium (Kv2.1) channels, which are related to hyperpolarization of neuronal membranes.37

Cannabinoids
Several reports have discussed the potential of cannabinoids, the major components of marijuana, in the management of seizures in animals. In a new study on patients with severe resistant epilepsy, in which 123 patients received a liquid cannabidiol product for 12 weeks, 48% of patients experienced a 50% or more seizure reduction and 10% were seizure free. At 4 month follow up, the median percent of seizure reduction was 52%.38

New developments
A number of compounds for the management of refractory epilepsy are currently going through different stages of development.

Drugs with modified structures include the analogs of levetiracetam, brivaracetam and seletracetam. These analogues have a 10-fold greater affinity to SV2A-binding site and show greater potency in animal models. Brivaracetam also has sodium-channel blocking activity and was associated with greater than 50% reduction in seizure occurrence in 52% of patients compared to 17% in the placebo group.12

Another example of derived drugs is valnoctamide, a valproate-like drug marketed as an anxiolytic. Valnoctamide shows higher anti-convulsant potency than valproate but its value in epilepsy is yet to be determined. Valrocemide, another derivative of valproate, does not cause embryo-toxicity in rats and rabbits.12 JZP-4, a lamotrigine analog with a safer pharmacokinetic profile, blocks voltage-gated sodium channels and calcium channels.

Felbamate is associated with the production of aldehyde toxic metabolites; hence the hydrogen atom is substituted with fluorine to prevent the yielding of these metabolites. Fluorofelbamate may inhibit NMDA receptors and affect sodium channels.

Oxacarbazepine, which is a derivative of carbamazepine, is synthetically modified to produce the R and S enantiomers of the monohydroxy derivative of oxacarbazepine, the metabolite responsible for the anti-convulsant activity. Licarbazepine is the mixture of both enantiomers, while eslicarbazepine
acetate is the S enantiomer. The latter drug, which works by blocking sodium channels, was approved by the FDA in 2013 as an add-on therapy for the treatment of seizures.

Since AMPA receptors play a role in the pathophysiology of epilepsy, targeting this receptor is a promising approach. Perampanel is an AMPA receptor antagonist that has been approved for marketing in Europe for the treatment of refractory partial-onset epilepsy.

A study published in 2012 showed that once daily dosing of adjunctive perampanel was effective in patients with uncontrolled partial-onset epilepsy. Alloprenanolone and its analog ganoxalone, which are neurosteroids, work as positive allosteric modulators for GABA-A receptor, showed promising results in refractory epilepsy.

Locasamide is an anti-convulsant that was approved by the FDA in 2007 as an adjunctive treatment of partial-onset seizures. This drug works by enhancing the slow inactivation of voltage-gated sodium channels. In a 485 patient trial, the reduction in seizure frequency was 35% in patients on locasamide against 21% in patients receiving placebo.

Adenosine, which is an endogenous anti-convulsant, has a role in seizure termination and its deficiency is a pathological hallmark in temporal lobe epilepsy. Therefore, it has possible therapeutic value and its augmentation is a rational approach. Due to systemic side effects, local delivery is desired. Several techniques are currently under investigation, including devices or engineered cells to release adenosine. A polymer adenosine implant made of silk fibroin protein is currently of great interest in epilepsy research.

**Conclusion**

In conclusion, drug-resistance is a major challenge in the management of epilepsy as it has negative medical, social, and economical impact. Multiple theories are proposed to explain the mechanism of resistance and several approaches are developed to overcome it. The management of refractory epilepsy includes pharmacological, surgical, and non-surgical methods like neuro-stimulation. Research about advances and measures to manage refractory epilepsy is continuously expanding.

**References**

1. The blockage of voltage-gated sodium channel is the primary action of

a) Phenytoin  
b) Carbamazepine  
c) Lamotrigine  
d) Topiramate  
e) All of the above

2. Which of the following drugs is a valproate-like anxiolytic drug that shows higher anticonvulsant potency than valproate?

a) Lamotrigine  
b) Topiramate  
c) Phenobarbitone  
d) Valnoctamide  
e) Ethosuximide

3. Which of the following is an AMPA receptor antagonist that is approved for treatment of refractory partial-onset epilepsy?

a) Topiramate  
b) Locasamide  
c) Perampanel  
d) Ganoxalone  
e) None of the above

Antidepressant as a prophylactic for Alzheimer’s?

Citalopram, a selective serotonin re-uptake inhibitor (SSRI) appears to deter the formation of amyloid plaques associated with Alzheimer’s disease, according to a recent study published in Science Translational Medicine.

Amyloid plaques and neurofibrillary tangles can be found in the brains of Alzheimer’s patients, but it is not clear if the plaques are precursors to neurodegenerative problems or an effect of them.

Citalopram is typically used to treat depression, anxiety, or obsessive-compulsive disorder. The same team who performed the current study had previously determined that SSRI s work through serotonin receptors on extracellular receptor kinase. This results in an up-regulation of alpha-secretase, an enzyme that cleaves amyloid, and therefore reduces its production. Every SSRI tested in mouse models was shown to lower amyloid concentrations.

The researchers first studied the effects of citalopram in the brains of mice. They found that citalopram prevented existing plaques from growing and reduced the formation of new plaques by about 78% In a randomized clinical trial involving 28 healthy people, 18-50 y old, the drug also prevented formation of beta amyloids in the cerebrospinal flu-
According to a randomised prospective trial published online last year in International Wound Journal (DOI: 10.1111/iwj.12395), wound healing in patients with diabetic ulcers is better with weekly applications of a dehydrated human amnion/chorion membrane allograft (EpiFix, MiMedx Group, Mariette, Georgia) compared with either a tissue-engineered skin substitute (Apligraf, Organogenesis, Canton, Massachusetts) or standard wound care. The healing was shown to be markedly faster, more complete, and cheaper with EpiFix. Studies have shown that the longer a diabetic foot ulcer remains open, the more likely the ulcer is going to get infected and that the patient is going to lose their limb leading to a shortened life span. The healing rate with EpiFix is claimed to be greater than 90%, and that it will heal the majority of wounds in an average of just over 2 weeks.

EpiFix is not the only amniotic-tissue product around. There are others in development that could be tested in diabetic foot ulcers, and a trial of a new cryopreserved umbilical-cord allograft for diabetic foot ulcers is also underway.

First comparative-effectiveness study of two wound-care products
In their paper, Charles Zelen and colleagues remarked that their study is the first multi-center randomised comparative-effectiveness study examining, side by side, the performance, outcomes, and utilisation of two approved advanced wound-care products (Apligraf and EpiFix) as a treatment for chronic lower-extremity diabetic ulcers.

Those whose wounds failed to reduce by at least 50% after 6 weeks of study enrollment were withdrawn from the study to seek alternative care.

At each study visit, patients underwent ulcer debridement if required and cleansing with a sterile normal saline solution. The ulcers were also measured and photographed and wound surface area calculated to evaluate treatment response.

At 4 and 6 weeks, complete wound healing occurred in a significantly greater percentage of patients treated with EpiFix compared with the other two modalities.

Lower costs with EpiFix
Healing rates were also significantly faster with EpiFix (P < 0.0001), with an estimated median healing time of 13 days for those receiving EpiFix compared with 49 days both for those receiving Apligraf and those receiving standard wound care.

The cost of the EpiFix product was reported to be much lower at $1669 per patient compared with $9216 per patient for Apligraf. Moreover, Apligraf, which is a skin product, is only good for a very
Predicting cancer drug response with personalised devices

Despite advances in analysing tumour biology, choosing effective therapies for cancer patients remains difficult. This is partly because there are still no timely, foolproof ways to test whether a patient will respond to a particular treatment. Addressing this issue, two independent teams, one at the Fred Hutchinson Cancer Research Centre in Seattle and another at MIT, have developed devices that can test a tumour’s response to multiple cancer drugs directly in the patient. Both devices are described in Science Translational Medicine. If validated in human clinical studies, the devices could be used before surgery to help identify the best course of individualised treatment for certain cancer patients. These devices are important because they capitalise on two aspects of the cancer problem. One is the fact that there are an enormous number of drugs that cannot be tested in all cancers using conventional trial methodologies. The second is that all cancers differ from one another.

Instead of serially treating patients until the most effective regimen is exposed, these platforms allow fast-forwarding to the most effective regimen that is revealed in the tumour in which the device is planted. The devices could also be used to select patients for clinical trials based on their localised responses to a given drug. The team at the Fred Hutchinson and Seattle Children’s Hospital, which developed one of the devices, called CIVO, has indicated that one small clinical trial testing the device could potentially replace several Phase 2 trials that test drugs in cancer patients without first identifying subpopulations most likely to respond to the treatment.

CIVO, a handheld device, can be used to deliver up to eight different cancer drugs (alone or in combination) into tumours close to the skin. Along with traceable fluorescent dye, the drugs are deposited in the centre and the edges of the tumour, enabling the analysis of drug reaction in different tumour microenvironments.

Following drug delivery, portions of the tumour can be excised and studied. The system is internally controlled—allowing direct comparisons of drug responses in the same tumour or in other words look for whether the cancer is inherently resistant to the drugs administered.
Thus far, the team have found that localized drug responses measured by the device are well-matched to the systemic responses to therapy observed in mouse models. An initial test in four cancer patients showed that the microinjection is well-tolerated and can induce localized responses that are easily tracked. Additional trials are now underway. The device can also be used to streamline preclinical studies. A study to test the efficacy of a drug, that used to take a lot of time and money, can now provide the same information with less expense.

Meanwhile, the team at MIT have developed an unnamed device that can deliver drugs to tumours deeper within tissues and be left implanted in the mass for up to 72 hours, allowing the drug or drug combinations to diffuse. The cylindrical device- 820 micrometers in diameter- is then removed with a coring needle and the surrounding tumour cells are analysed. So far, the team has confirmed that the local drug responses within tumour micro-environments seen in mouse models of melanoma, prostate, and breast cancer mirrored the systemic responses observed in the same models. The team is now working to further miniaturize the device and planning for clinical trials. The end goal is to provide oncologists with treatment recommendations within a day. This technology is ideally suited for cancer types, such as lymphoma and breast cancer, for which there are multiple FDA-approved therapies or combination regimens.

Both devices have their limitations. For one, they’re not at this time meant to evaluate long-term drug response or resistance. And they can’t be used to evaluate local response to therapies delivered as prodrugs, which must be activated in the liver. Further, the devices are designed to treat the bulk of the tumour mass and may not reach sparsely distributed pockets of cancer cells.

However, these devices show greatest potential for evaluating the potential efficacy of both approved and investigational cancer treatments that may be effective for a given cancer patient, but may not have been tested in a conventional clinical trial.

References:

**ASCO’s top five over-used cancer tests and treatments**

The American Society of Clinical Oncology (ASCO) issued its second “Top 5” list of tests and treatments that are routinely used by oncologists despite a lack of evidence that they are cost effective or beneficial to patients.

The list, part of the “Choosing Wisely” campaign sponsored by the American Board of Internal Medicine, is aimed at encouraging oncologists to consider other options for high-cost or unproven tests and therapies. For example, expensive antiemetics may be justified for patients taking highly emetogenic chemotherapy, but patients at lower risk for nausea and vomiting typically do just as well with older, less costly drugs, according to the recommendations published in the Journal of Clinical Oncology (JCO).

The following “Top 5” recommendations are meant as “evidence-based advisories” for oncologists and patients to consider when creating individualized treatment plans, according to the JCO authors:
1. Do not give anti-nausea drugs (anti-emetics) to patients starting on chemotherapy regimens that have a low or moderate risk of causing nausea and vomiting. Reserve these expensive drugs for patients taking chemotherapy that has a high potential to produce severe and/or persistent nausea and vomiting.

2. Do not use combination chemotherapy instead of single-drug chemotherapy when treating an individual for metastatic breast cancer unless the patient needs urgent symptom relief. Give chemotherapy drugs one at a time in sequence, which may improve a patient’s quality of life without compromising overall survival. Consider combination therapy in situations where the cancer burden must be reduced quickly because it is causing significant symptoms or is immediately life threatening.

3. Avoid using advanced imaging technologies (PET, CT, and radionuclide bone scans) to monitor for a cancer recurrence in patients who have finished initial treatment and have no signs or symptoms of cancer. Using PET or PET-CT to monitor for cancer recurrence in asymptomatic patients who have completed treatment and have no signs of disease has not been shown to improve outcomes or survival and can often lead to false positive results.

4. Do not perform PSA testing for prostate cancer screening in men with no symptoms of the disease when they are expected to live less than 10 years. Studies have shown that PSA screening in this population does not reduce the risk of dying from prostate cancer or from any cause. Such testing could lead to unnecessary harm, including complications from unnecessary biopsy or treatment for cancers that may be slow growing and not ultimately life threatening.

5. Do not use a targeted therapy intended for use against a specific genetic abnormality unless a patient’s tumor cells have a specific biomarker that predicts a favorable response to the targeted therapy. Targeted therapy drugs are far more expensive than other therapeutic options, and many carry the risk of significant adverse effects.

**Possibly fatal blood clots with Ponatinib**

The FDA issued a safety alert and reported an investigation into a high rate of thrombosis and other cardiovascular events in patients taking ponatinib (Iclusig, Ariad Pharmaceuticals) for chronic myeloid leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL).

Ponatinib, approved in December 2012, already contained labeling warnings about blood clots. In trials that led to approval, the rate of serious arterial clots was 8%, venous blood clots were reported in 2.2% of patients.

New data from the PACE trial show that after a median follow-up of 24 months, serious arterial thrombosis occurred in 11.8% of patients receiving the drug. Cardiovascular events were most common (6.2%), followed by cerebrovascular (4%) and peripheral vascular events (3.6%; some patients had more than one type of event). The rate of serious venous occlusion rose to 2.9% of patients. According to the company that makes ponatinib, the increased totals of adverse events has not increased the incidence rate of arterial thrombotic events when normalized to the duration of treatment. The rate in the original analysis was 10 events per 100 patient-years, and has actually now dropped to 9.6 events per 100 patient-years. Still, non-serious plus serious arterial and venous events have occurred in approximately 20% of patients treated with ponatinib.

Patients currently enrolled in the EPIC trial comparing ponatinib and imatinib in newly diagnosed CML (ponatinib is currently approved only in CML that has proven resistant or intolerant to previous tyrosine kinase therapy) will have their dose of...
FDA evaluating the potential risks of using codeine cough-and-cold medicines in children

The FDA is investigating the possible risks of using codeine-containing medicines to treat coughs and colds in children under 18 years because of the potential for serious side effects, including slowed or difficult breathing.

It is recommended that parents and caregivers who notice any signs of slow or shallow breathing, difficult or noisy breathing, confusion, or unusual sleepiness in their child should stop giving their child codeine and seek medical attention immediately by taking their child to the emergency room.

Parents and caregivers should always read the product label to find out if a medicine contains codeine and talk with their child’s healthcare professional or a pharmacist if they have any questions or concerns. Health care professionals should continue to follow the recommendations in the drug labels and use caution when prescribing or recommending codeine-containing cough-and-cold medicines to children.

Codeine is a specific type of narcotic medicine called an opioid that is used to treat mild to moderate pain and also to reduce coughing. It is usually combined with other medications in prescription and over-the-counter (OTC) cough-and-cold medicines. Codeine works by changing the way the brain responds to pain and by decreasing the activity in the part of the brain that causes coughing.

In the body, codeine is converted to the opioid morphine. Some people convert codeine to morphine faster and more completely than usual, resulting in higher amounts of morphine in their blood. High levels of morphine can result in problems, including breathing difficulty that may lead to death.

Children, especially those who already have breathing problems, may be more susceptible to these serious side effects. In 2013, FDA warned against using codeine in children who recently had surgery to remove their tonsils and/or adenoids.

In April 2015, the European Medicines Agency (EMA) announced that codeine must not be used to treat cough and cold in children under 12 years, and that codeine is not recommended in children and adolescents between 12 and 18 years who have breathing problems, including those with asthma and other chronic breathing problems.

Source:
http://www.fda.gov/Drugs/DrugSafety/ucm453125.htm
Assessment drives learning

In its efforts to improve student performance and learning habits, the Faculty of Pharmacy has been exploring ways in which this can be done alongside better assessment procedures that promote competency-based rather than the more traditional knowledge-based education. This is particularly important in a vocational degree such as pharmacy, where graduates need to integrate the knowledge they have gained, with their experiential training, in the healthcare environment.

Developing an appreciation that knowledge is only as good as its application is as much a matter for the instructor as for the instructed, and should be built into assessment.

Assessment has to be aligned with curricular outcomes. Accordingly, programmatic assessment is emerging as a structured way of considering assessment as part of a learning strategy, rather than as an imperfect but necessary tool to determine the extent to which students have achieved their course learning objectives. It includes periods of formative assessment and feedback to allow students to pursue the development of their competencies. Student grading is then based on a collection of assessments (data points) measured on several activities with appropriate examination methods.

With this approach, assessment thus becomes part of the curriculum and learning activities.

With the assistance of an external consultant from Maastricht University, Prof. Erik Driessen, academic staff from the Faculty have developed a model for an integrated active-learning and assessment framework, that will guide the preparation and delivery of the courses that are part of the Faculty’s intended transitional post-baccalaureate add-on PharmD prior to the introduction of an entry level PharmD program.

This framework dictates that both knowledge and competency development will be assessed by methods that are aligned with the learning activities. It is important to bear in mind that, although knowledge alone is not sufficient to be competent, it is a necessary pre-requisite and therefore must be effectively learnt and assessed.

The effectiveness of workplace-based assessment, is an essential factor to ensure competency. The use of “entrustable professional activities” (or EPA) as a means of allowing preceptors to evaluate students requires sufficiently qualified personnel at experiential training sites. EPA are emerging as the standard to translate competency assessment (characteristic of the professional) into the real world (activities of the professional).

By formulation of a series of standardized EPA, future preceptors will have a framework and clear guidelines to assess the students as they engage in meaningful activities in the workplace.

Another aid to both guided teaching and assessment is the use of an electronic portfolio to keep track of the progress of students in the different competency dimensions identified as crucial to become competent pharmacists. A flexible portfolio portal has been developed in Maastricht, which may provide a suitable model to help achieve our educational goals.

As we move forward in our aim of improving pharmacy education in Kuwait, supporting tools, like a portfolio, will be introduced to bring technology into education in a relevant manner.

P Moreau,
Faculty of Pharmacy, Kuwait University
**New Pharmaceutical products approved from May to October 2015**

- Advagraf Capsules 0.5,1,3mg; Tacrolimus-0.5,1,3mg; Astella/Ireland
- Altargo Ointment; Retapamulin-10mg; Glaxo Group Ltd.- UK
- Avomin Tablets 1mg; Anastrozole-1mg; Geneapharm S.A/ Greece
- Basaglar Sln. for Injn. cartrige 100 IU/MI; Insuline glargine-300 U; Eli Lilly Gmbh/Austria
- Basaglar Sln. for Injn., PFP 100 IU/MI (Kwik pen); Insuline glargine-300 U; Eli Lilly Gmbh/Austria
- Bilaxten Tablets 10,20mg; Bilastine-10,20mg; Jazzera Pharm. Ind/ KSA
- Bisoprol Tablets 5mg; Bisoprolol-5mg; The United Pharm.Mfg. Co. Ltd/Jordan
- Cefotaxime Norman 1g Powd. & Solvent for Injectable Sln. (IM); Cefotaxime-1g Lidocaine hydrochloride 40mg in 4ml Water for Injection; Lab. Noarmon S.A/ Spain
- Cefotaxime Norman 1g Powd. & Solvent for Injectable Sln (IV); Cefotaxime -1g Water for Injn- 4ml; Lab. Noarmon S.A/ Spain
- Cefotaxime Norman 500mg Powd. & Solvent for Injectable Sln (IV); Cefotaxime -500mg Water for Injn -2ml; Lab. Noarmon S.A/ Spain
- Cerebrolysin Sln. for Injn. 215.2,1076 and 2152mg/ml; Cerebrolysin Conc.215.2,1076 and 2152mg/ml; Ever Neuro Pharma Gmbh - Austria
- Clopidocor Tabs. 75mg;Clopidogrel-75mg; Sandoz Pharm. Gmbh-Germany
- Clottafacl Pwdr. & Solvent for Sln. for Injn. 1.5g/100ml; Human Fibrinogen-1.5g; LFB Biomedicaments -France
- Cosentyx Sln for Injn. In pre-filled SensoReady (pen) 150mg/ml; Secukinumab (rDNA)-150mg; Novartis Phama Schweiz AG/Switzerland
- Cosentyx Sln. for Injn. PFS 150mg/ml; Secukinumab (rDNA)-150mg; Novartis Pharma Schweiz AG/Switzerland
- Creon 25000, 40000 Capsules; Pancreatin 300,400mg; Abbott Arzneimittel GmbH/Germany
- Desloratadine Normal Oral Sln. 0.5mg/ml; Desloratadine 0.5mg; Laboratorios Normon S.A/Spain
- Dimentile Tabs. 5,10mg; Donepezil HCl-5mg; Tabuk Pharm/ Saudi Arabia
- Duphalac Sticks 667 g/L; Lactulose
- Emipride Tabs. 2,3mg ;Glimepiride-2mg; Globalpharma Co. LLC-UAE
- Finastr Tablets 5mg; Finasteride-5mg; Geneapharm S.A.Greece
- Folotyn Sln. for Infn. 20mg/ml; Pralatrexate-20mg; Mundipharma Medical Co.Switzerland
- Ginenorm Sln. for Vaginal use 0.1%; Ibuprofen-0.1g; Aesculapius Farmaceutici C.R.L/ Italy
- Glopressin Sln. for Injn. 0.1mg/ml; Terlipressin-0.85mg; Ferring Gmbh/Germany
- Harvoni Tabs. 90mg/400mg; Ledipasvir-90mg Sofosbuvir-400mg; Gilead Sciences Intl. Ltd/ UK
- Imbruvica Capsules 140mg; Ibrutinib-140mg; Janssen-Cilag Intl. N.V/ Belgium
- Irrgeben Plus 150/12.5mg; Irbesartan-150mg Hydrochlorothiazide-12.5mg; Geneapharm S.A/Greece
- Irrgeben Plus 300/12.5mg; Irbesartan-300mg Hydrochlorothiazide-12.5mg; Geneapharm S.A/Greece
- Irrgeben Plus 300/25mg; Irbesasran-300mg Hydrochlorothiazide-25mg; Geneapharm S.A/Greece
- Jofen Oral Drops; Ibuprofen-50mg; Jerash Pharm.Ltd./ Jordan
- Kyprolis Pwd. For Sln. for Injn. 60mg/Vial; Carfilzomib-60mg; ONYX Pharma. Inc. – USA
- Laprix Tablets 10mg; Olanzapine-10mg; Tabuk Pharm./ Saudi Arabia
- Levonic Sln. for IV Infn. 500mg/100ml; Levofloxacin-500mg; Jazzera Pharm. Ind/ KSA
- Levonic Tablets 500mg; Levofloxacin-500mg; Jazzera Pharm. Ind/ KSA
- Levotab Tablets 500mg; Levofloxacin-500mg; Globalpharma Co. LLC-UAE
- Likacin Sln. for IM/IV Inj. 250mg/2ml; Amikacin-250mg; Lab. Biochimico Farmaceutici Lisapharma S.p.A/Italy
- Likacin Sln. for IM/IV Inj. 500mg/2ml; Amikacin-500mg; Lab. Biochimico Farmaceutici Lisapharma S.p.A/Italy
- Mofilet Tablets 500mg; Moxifloxacin Mofetil-500mg; Emcure Pharm. Ltd/India
- Moncas Chewable Tabs. 4,5,10mg; Montelukast-10mg; Geneapharma SA/Greece
- Motrinex Chewable Tabs. 4,5mg; Montelukast -4,5mg; Dar Al Dawa Dev. & Inv. Co. Ltd/ Jordan
- Mucinex Maximum Strength Bilayer Tablets 1200mg; Guaifenesin-1200mg; Reckitt Benckiser USA.
Answers to: Test your knowledge

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

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