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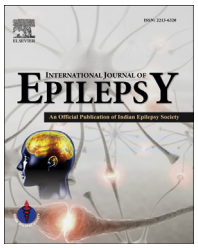

Review Article

Application of mobile phones in epilepsy care

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ABSTRACT

Objectives: To evaluate the applications of mobile phones in the day to day care of epileptic patients as a diagnostic, prognostic and therapeutic tool.
Methods: Detailed search of various mobile applications in the field of epileptology was made in MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, CINAHL, LILACS and corresponding developer websites of mobile applications were also looked into regarding their technical specifications and user friendliness.
Results: A plethora of apps are available across various mobile platforms especially Android, iOS and Windows. Careful selection and application of such apps by both the healthcare providers, the epileptic patients and their caregivers with proper understanding of their potential benefits as well as limitations will result in better diagnosis, prognosis and treatment of epilepsy.
Conclusion: The field of medicine is rapidly inculcating advanced cutting edge technologies for better diagnosis of diseases and better targeted therapy to such diseases. Hi tech electronic gadgets, in particular, are now becoming part and parcel of patient care in many specialties. The advent of the modern portable computers has revolutionised almost every specialty. The field of mobile technology is advancing with a break neck pace, with increase in mobile subscribers, advanced handsets practically like digital personal assistants with advanced capabilities. The possibilities of using such rapidly evolving mobile technology in the field of medicine are endless. This article explores such possibilities in the field of epileptology after analysing the current and existing applications of mobile phones in care of the epileptic patients worldwide.

1. Introduction

The field of medicine is rapidly inculcating advanced cutting edge technologies for better diagnosis of diseases and better targeted therapy to such diseases.[1] Hi tech electronic gadgets, in particular, are now becoming part and parcel of patient care in many specialities. The advent of the modern portable computers has revolutionised almost every speciality.

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Advanced robotics have revolutionised the field of surgery.[2] Robotically assisted surgical systems are now being used for prostatectomies,[3] several gynaecologic procedures and even cardiac surgeries. Remote surgery, minimally invasive surgery, unmanned surgery have now become possible due to advances in robotics.[4] Now surgeries are possible with better precision, miniaturization, smaller incisions and subsequently reduced pain and blood loss resulting in a quicker healing time and reduced hospital stay. Contrary to the popular belief that more advanced the technology – the more the cost of the surgery, robotic surgery has actually reduced the cost of patient care in some instances, due to decreased number of days spent in hospital, reduced number of blood transfusions, decreased use of analgesics and antibiotics due to quicker healing, etc.

In the field of epileptology, technological advancements have already improved patient care in innumerable ways. The archaic and bulky analog electroencephalography (EEG) machines, which used pen and paper for output, required bundles of paper to just record EEG data from a single individual. The effort that an epileptologist had to put in to go through such unorganised and scrambled EEG data made EEG analysis cumbersome and was prone to erroneous interpretation in many instances. Now computerised digital recording of EEG along with the ease with which such data could be transmitted across the internet to anyone in the globe has revolutionised EEG monitoring and has practically eliminated the difficulties one had to face in EEG analysis.[5] Digitization of EEG has paved the way for EEG monitoring now in emergency rooms, intensive care units and operating rooms with automatic data trending. Digital EEG also has the advantage of montage reformatting and quantitation of parameters with an increased spatial and temporal resolution, thus enabling us to manipulate the captured digitized EEG data applying various filters, changing the sensitivity, sweep speed, etc….

Mobile technologies are increasingly being used to transform health systems by opening novel and innovative ways to improve health care delivery. Today a mobile phone (smartphone) allows access to internet and healthcare applications, store data, play and record audio and visual media. By 2015, 500 million mobile users (which include health care professionals, consumers, and patients) worldwide are likely to be using a health care application. The safety and effectiveness of mobile devices, medical apps are the public health responsibility of FDA.

Mobile phones are being extensively used even in Low and Middle Income Countries (LAMIC) to capture the seizure event and it may serve like a physician having witnessed the event. This certainly may be of help for proper classification of seizure semiology and appropriate therapeutic directions. This tool may become a gold standard as compared to earlier thinking that the history was a gold standard in epilepsy. There are many applications (software programmes/apps) developed specifically to assist people with epilepsy and their caregivers. These applications have seizure management tools including seizure diary, seizure tracker, vital first aid information and information on when to call an ambulance etc. Apart from these applications, mobile phones with GPS (Global Positioning System) technology can be programmed to raise an alarm if the unit detects any adverse events like a fall in an epilepsy patient which thus helps to locate the patient by sending an alert to the response centre and thereon to the caregiver. In poor countries, smartphone EEG is under clinical trial which uses smartphone and simple electrode skullcap to monitor brain signals. Thus these mobile phone epilepsy solutions can be highly beneficial in effective and timely care of the epilepsy patients.

The field of mobile technology is advancing with a break neck pace. Number of mobile network subscribers has multiplied several fold in the recent years and is expected only to increase in the future. As of March 2014, the number of cell phones in India alone is 904.51 million with a monthly increase of 1.05 million.[6] Especially mobile code division multiple access (CDMA) technology and Global system for mobiles (GSM) has given rise to advanced handsets which have now practically become digital personal assistants to an individual. Advances in the smartphone operating systems like Android, iOS, Windows Mobile, etc. have made such handsets more versatile and user friendly. They have evolved from being just a two way paging device to being mobile phones with GPS navigation device, web browser, instant messenger, handheld game console and much more. 3G and 4G networking, tablet PCs and smartphones have just taken complete control of an individual's life. The possibilities of usage of such rapidly evolving mobile technology in the field of medicine are endless. But, on the other hand, there may also be certain limitations as to if these applications/technology (that are not approved by a regulatory agency) don't work as intended or are not interpreted correctly by the user/caregiver/healthcare professional which can pose a great risk to the health of the patient. This article will explore these possibilities in the field of epileptology by analysing the current and existing applications of mobile phones in care of the epileptic patients worldwide. 'Mobile Epileptology' could be the future of better care of such patients.

2. Mobile phones apps in epilepsy care

In the field of healthcare in general, the usage of mobile phones and mobile apps promises to deliver individualised highly targeted therapies tailored to a given patients requirements.[7]

Broadly, in epilepsy care, mobile phone apps can be useful in the hands of the epileptic patients, their caregivers or the healthcare professionals themselves. Innumerable number of such apps are now available for such purposes and a brief overview of them is illustrated below (Fig. 1).

2.1. *Mobile phones apps for epileptic patients and their caregivers*

Currently a variety of apps like the ***'epilepsy society app'*** (Fig. 2) ***or 'my epilepsy diary'*** (Fig. 3) are available in the market which can be used as **seizure diaries** allowing the patient or the caregiver to record the time of the seizure, length and type of an attack, timing and dosage of medication taken prior to the attack, etc … Additional information which can be helpful in epilepsy management like the environment and circumstance in which the attack occurred, time in hours spent in sleep the

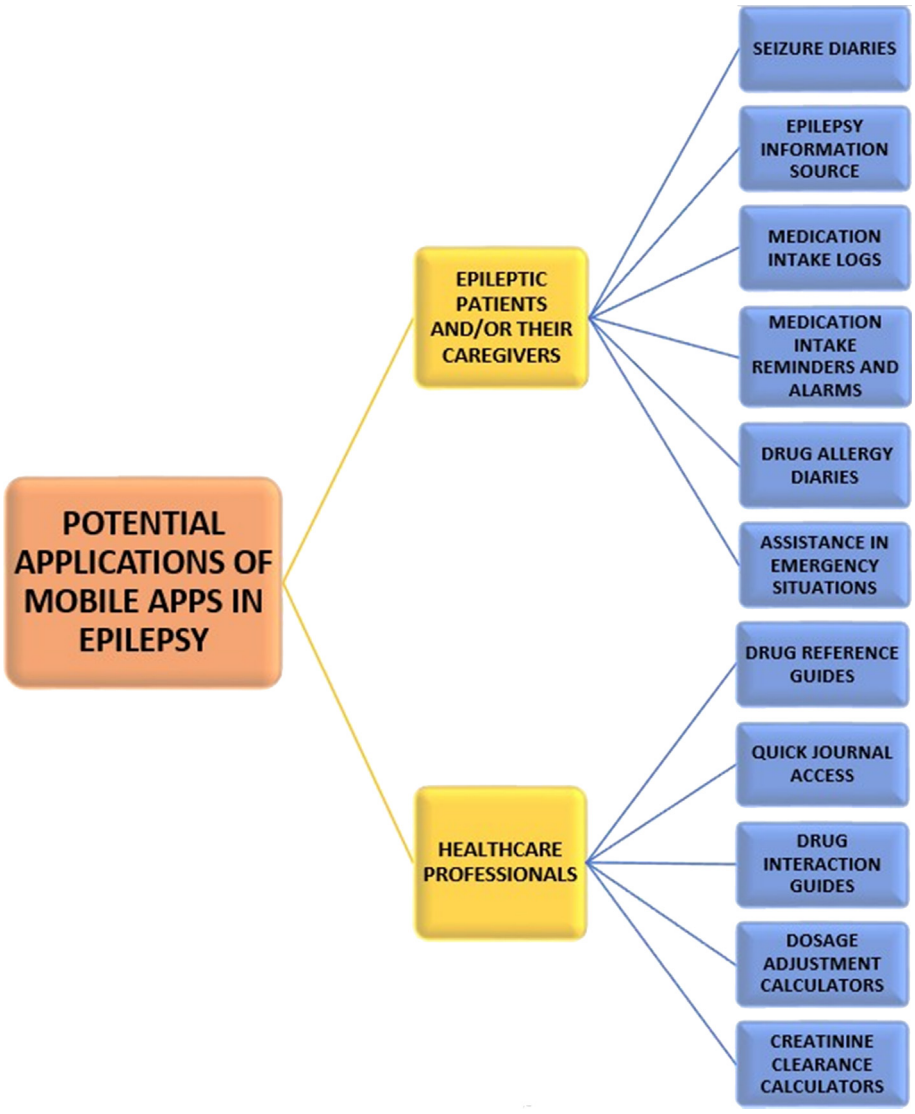

Fig. 1 – Applications of mobile phones in epilepsy care.

previous night, dosage, timing and frequency of alcohol intake, details of the last menstrual cycle, correlation with lunar calendars, dosage and timing of any other medication intake like antihypertensives and antidiabetics, timing of the last meal before the attack, etc … can enable the patient to record all the relevant data which will be of great assistance to the physician. This information can then be sent to the physician taking care of that patient through SMS or Email. Instant access to the mobile number of the physician in case of an emergency is also possible with some of the apps. The information provided by such apps not only helps in better management but also in diagnosing a particular type of epileptic syndrome that the patient would fit into depending upon the pattern and frequency of seizures that a particular patient experiences and thus help to choose an appropriate drug therapy for better seizure control.

Apps like ***'epilepsy vault'*** (Fig. 4) can provide epileptic users and their caregivers with basic information regarding epilepsy and its management thus increasing awareness regarding the illness. For improved drug compliance, awareness regarding the illness is absolutely critical from the patients' perspective. Knowledge regarding their illness is now freely available across the internet for most of the epileptics through mobile web browsers or through mobile phone apps.

Antiepileptic drug incompliance by the patient is one of the primary hurdles that a neurologist faces to make a patient seizure free. The risk of having a seizure in an epileptic is inversely related to his or her drug compliance, as common sense would suggest.[8] There are several factors which govern drug compliance. Thus the patients drug intake history, history of any drug incompliance if any, time and date of the dosage skipped and the reasons behind it are all highly valuable information that every neurologist strives for. Information which may seem mundane and 'not worthy to be mentioned to a neurologist' for the patient or the care-giver may in fact, be the most important data required by the neurologist to tackle drug incompliance. Many times epileptic patients especially those with generalised seizure attacks tend to forget such information, especially after an episode of a seizure with loss of consciousness. Such valuable data will

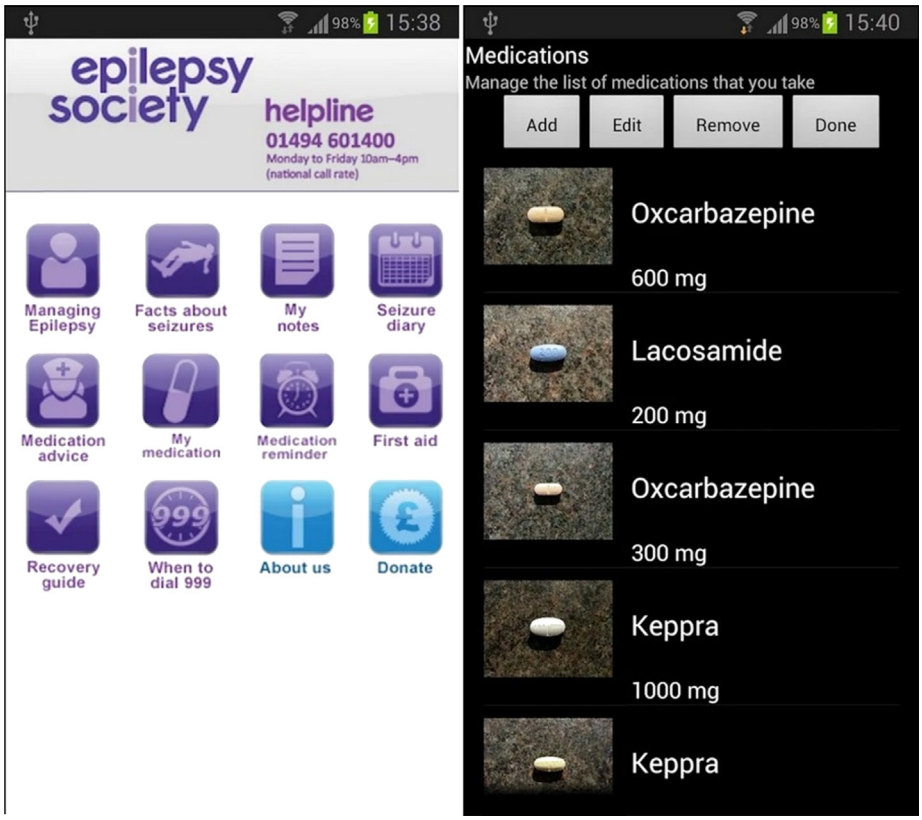

Fig. 2 – 'Epilepsy society' app. Courtesy: Epilepsy Society, App developer. Email: Ben.O'Keefe@epilepsysociety.org.uk.

forever be locked away from the neurologist deep inside the patients' mind. There are a variety of mobile apps which come in handy to deal with this obstacle. Several apps are now available in the market in which the patients may be motivated by the neurologist and the care-giver to record the details regarding their drug intake dose by dose. Apps like the '*Dosecast – Medication Reminder*' (Fig. 5), '*medication log*' or '*personal medication record*' can be used by the patient to record the frequency, dosage and timing of medications that they are currently on. Some apps also allow patients to record any allergic reaction to medications that occur during the course of treatment which can be of great help for the physicians to choose the appropriate drug for the given patient. Usage of such apps in conjunction with the seizure diaries will be

Fig. 3 – 'My epilepsy diary' app. Courtesy: Irody Inc., App developer. Website: www.Irody.com.

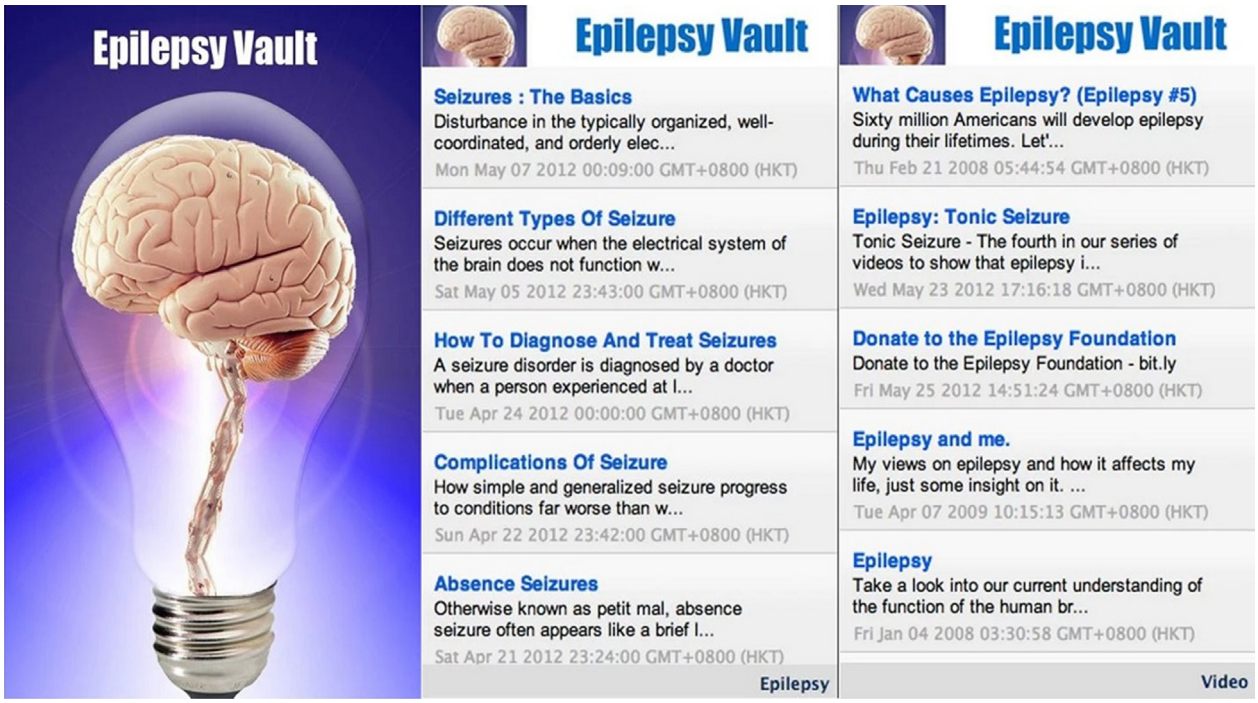

Fig. 4 – 'Epilepsy vault' app. Courtesy: Ellery Leung, Epilepsy vault App developer. Email: alucard001@gmail.com.

helpful to change or adjust the dosage of the antiepileptic medications. Such apps may also provide users with valuable information like what to do as an emergency measure in case of an adverse event due to a particular medication, even before reaching out to the doctor. Some of the apps also warn patients regarding potential drug interactions in case a patient takes anti-epileptic medication along with any other medication like oral contraceptive pills, etc.

These apps also help the patient remember to take the antiepileptic drugs on time by providing the user with a visual and an auditory reminder when it is time to take the drugs similar to an alarm clock. Patients' treatment compliance, which is highly crucial as mentioned above for an effective antiepileptic drug therapy can greatly be enhanced with the assistance of such apps.

In addition to the above mentioned applications, mobile phones which invariably have an attached camera can be used by caregivers to record a video footage of an ongoing seizure attack. An exact description of the seizure semiology is difficult to obtain from most of the epileptics or their caregivers, especially in case of bizarre complex partial seizures and in patients with multiple seizure types. It is in this situation that the ability of mobile phones to record video and to stream it across mobile network to a neurologist anywhere in the world comes really handy. Episodes other than prototypical seizures like any abnormal behaviour, anger outbursts, aggression, tremors, myoclonic jerks, etc., which are prone to occur in some patients can also be recorded by the caregivers to aid their management by the neurologist in charge. In addition, the saved video file will also have a detailed description of the time and day of the recorded event, length of the event, and in some mobile phones, a tag to the specific location in which the event was recorded will also be available to the neurologist in case the caregivers lose track of such data in a given patient. Hence, without a doubt, mobile phones in the hands of the patients or their caregivers can greatly enhance diagnosis and management of epilepsy.

2.2. *Mobile phone apps for healthcare professionals*

In the hands of healthcare professionals mobile apps regarding epilepsy generally provide faster access to well organised information regarding diagnosis and management of epilepsy. It has always been a nightmare for the physicians to keep track of the innumerable drugs available in the market in different combinations available under different generic and brand names. To choose the best among them tailored to cater to specific needs of a given patient with cost effectiveness in mind can be practically impossible in busy day to day practice of a neurologist. Some apps like '***Medication guide***', '***Generic drugs encyclopedia***' or '***pocket drug reference***' can be used by the physicians for information regarding a particular drug, or even for choosing an appropriate drug in a particular situation and can be a boon for busy practitioners. Furthermore, several potential adverse drug interactions can be avoided by careful usage of such apps for epileptic patients taking medications for other comorbid illnesses. Apps like '***drug interaction***' or '***drug interactions (A–Z)***' are specifically designed to cater to such needs of the neurologists.

Calculation of dosage of a given anti-epileptic medication of choice in a particular patient can be really cumbersome. Several apps are now available which make such calculations easier for the neurologists. In patients with renal impairment, dosage of many anti-epileptic medications with renal excretion need to be adjusted. Calculation of creatinine clearance in such patients is of paramount importance to make such

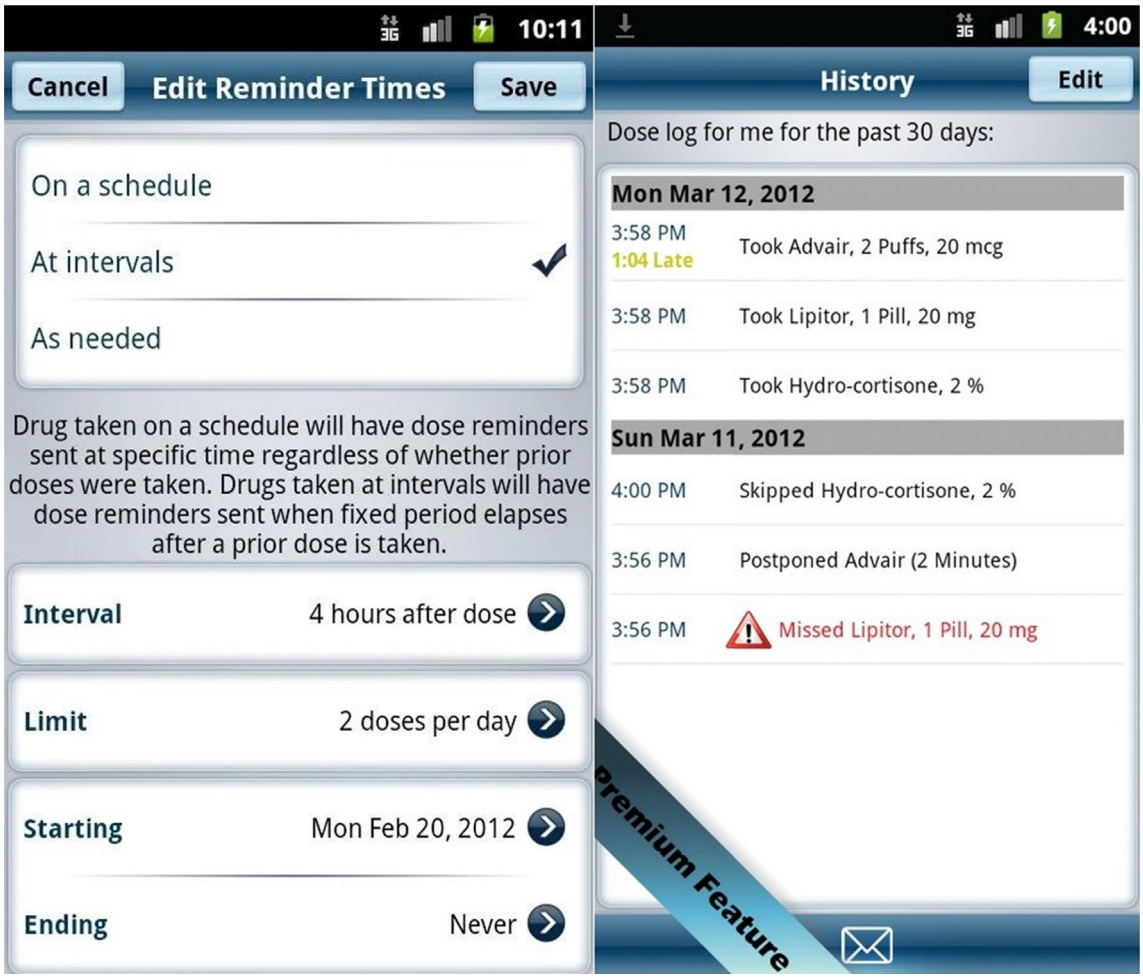

Fig. 5 – 'Dosecast – medication reminder app'. Courtesy: Montuno software, LLC, App developer. Email: jlevene@montunosoftware.com.

adjustments. Apps like ***'creatinine clearance calc'*** or ***'creatinine clearance fast'*** (Fig. 6) come in handy in such situations.

Similarly, in case of epileptics with other comorbidities like hepatic impairment, hypertension, diabetes mellitus, renal calculi, glaucoma, cardiac illnesses, etc. dosage adjustment is made easier with mobile phone apps. In addition, access to various journals regarding recent advances is made more organised and easier by many mobile phone apps, helping the physician to stay up to date in the concerned speciality. Mobile phone browsers have now practically eliminated the time wasted to go through volumes of reference books to obtain data pertinent to a particular clinical situation, in day to day practice of a busy physician. Almost every medical journal is accessible through mobile platforms now which always is an added advantage to any healthcare professional, especially in the dynamic and ever changing field of epileptology.

3. Mobile phones in epilepsy detection

Mobile phones can also be used for epilepsy detection through motion detectors, live EEG monitors galvanic skin conductance detectors and patient controlled triggers (Fig. 7). In addition to the mobile phone apps which can be used in epilepsy care outlined above, a variety of applications and devices are now available in the market like the ***'epdetect'*** (Fig. 8) ***or 'smartmonitor's Smartwatch'*** which can be used to detect a seizure in progress. Such gadgets make use of a mobile phone's inbuilt gyroscopic sensors, accelerometers and GPS modules for detecting a seizure and locale of seizure. Epdetect employs digital signal processing for detecting seizures. Movements in the frequency of 2–5 Hz lasting at least for 10 s are considered as potential seizures and any movement falling outside this criteria is ignored thus increasing the sensitivity and specificity of predicting seizures. Smartwatch is actually a wristwatch which can be worn by a patient containing a GPS module and a proprietary accelerometer/gyroscopic sensor inside to detect the excessive and repetitive movements that occur during seizures. It then records the time, duration and location of such events and transmits that information via Bluetooth to app on the smartphone of the user. This can then be transmitted to anyone around the world instantly, particularly to the physician or to the caregiver who will instantly know the location and status of the patient thus averting any tragic delays in management, if the patient loses consciousness, thus adding an additional layer of safety to the epileptic wearer. The watch also features physical buttons on the

Fig. 6 – 'Creatinine clearance fast' app. Courtesy: Gemini software, App developer. Email: franc.gemelli@gmail.com.

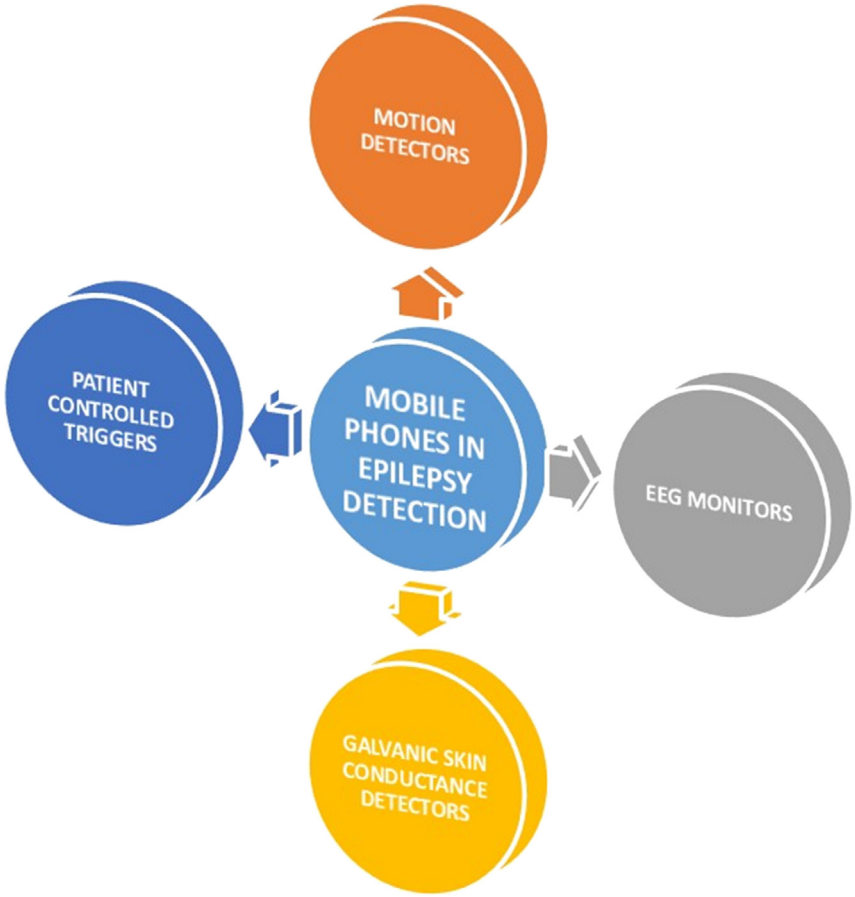

Fig. 7 – Mobile phones in epilepsy detection.

Fig. 8 – Epdetect – uses motion sensors to detect epilepsy.

side that allow users to cancel a false alert or to manually send a false alert message with a single press. The sensitivity of the seizure detector can be adjusted which allows the Smartwatch to be adjusted to an individual's need.

Aside from safety that comes with wearing the watch, it also provides valuable information to neurologists over the long term. When and where seizures take place is information that doctors find useful, and it can be very difficult for patients to recall such information after an event. Such devices can provide doctors an accurate log of a patient's episodic history that they wouldn't be able to obtain otherwise.

Some devices like the ***'Affectiva's Q Sensor'*** use changes in galvanic skin response as opposed to motion detection to detect a seizure. The increase in skin conductance could predict the occurrence of a seizure and the degree of conductance is said to be proportional to the severity of an attack and to the degree of postictal EEG suppression.[9] Such devices provide an exciting possibility of delivering an objective measurement scale to quantify the severity of seizure episodes.[10] Patients' or the care-givers' history regarding the severity of such events can be notoriously misleading practically nullifying any meaningful derivations that can be made out of them. Neurologists currently rely primarily on the frequency and duration of such attacks to titrate the antiepileptic drug dosage. An objective measure of severity of the episodes would be an added tool to guide such titrations more accurately according to the patients' requirements. SMART (Seizure Monitoring And Response Transducer) Belt also uses a similar principle to detect seizures.

4. Real time eeg monitoring

Wireless EEG monitoring devices are now available for better patient comfort and enable 24 hour ambulatory monitoring of epileptic patients a lot more feasible. Fully functional EEG headsets with wireless connection to a smartphone for continuous EEG monitoring have been demonstrated to be practically possible.[11] Currently research is in progress regarding the feasibility of such devices for widespread use. Such devices used in conjunction with the above mentioned devices and apps could provide a more sensitive, specific and reliable way to detect and monitor seizures in a given epileptic patient.

5. Future perspectives

A lot of exciting possibilities exist in the application of mobile technology in care of patients with epilepsy. A multidisciplinary approach involving the collaboration of neurologists, electronic and electrical engineers, pharmaceutical companies and more importantly the patients themselves would be required to make such possibilities a reality.

5.1. *Automated drug monitoring devices*

Similar to continuous glucose monitors (CGM) currently available in the market, continuous antiepileptic drug monitoring devices could be possible in the near future. Such devices when integrated with a parenteral drug delivery system and to the user's mobile phone would ideally eliminate current hurdles in epilepsy management like drug incompliance, drug over dosage and associated adverse reactions, inadequate dosage, infrequent dosage, narrowness of the therapeutic window, etc. Such devices if connected wirelessly to a mobile device would also enable real time monitoring of the drug levels in the patient's blood by the neurologist and adjust the drug dosage accordingly.

5.2. *Automated antiepileptic drug delivery devices*

Newer methods of antiepileptic drug delivery is the need of the hour. Intense research is underway exploring various possibilities to find a more reliable, consistent, cost effective, safe and dependable method of drug delivery as an alternative to the current oral regimes which are highly dependent on patients' motivation and cooperation. Skin patches, slow release oral, buccal, nasal, rectal forms, liposomes are all being thoroughly investigated.[12,13] Direct and continuous drug delivery via an infusion pump parenterally or more specifically, directly into the seizure focus via implanted infusion catheter could be the answer and could become a reality in the near future getting rid of all the demerits of the current antiepileptic regimes.[13,14]

5.3. *Comprehensive seizure detection, eeg monitoring, drug monitoring and drug delivery devices integrated to a mobile device*

This could be called as the holy grail of epileptology and might seem unrealistic and far-fetched at the first glance (Fig. 9). But with the current mobile technology available, it is definitely within our reach. The initial cost of such comprehensive devices could be high, but with mass production, widespread usage of such devices could become possible. Motion detectors and Galvanic skin response detectors could be worn by the patient in the form of a watch connected wirelessly to the patient's mobile phone which in turn would function as a central processing unit of the entire system. Continuous antiepileptic drug level monitors would provide round the clock data of the drug levels in the patient's blood to the mobile phone. The mobile phone would also receive constant information through the real time EEG monitors worn by the patient as a cap or from implanted intracranial electrodes of the patient. The afferent information sent by the motion detector, galvanic skin response detector, drug level monitor and EEG monitor would be integrated and processed by the mobile phone. The efferent information from the mobile phone would then be transmitted real – time wirelessly via Wi-Fi or Bluetooth to the continuous drug infusion device delivering the drug directly through implanted catheters to the seizure focus or into the patient's blood stream. Thus adjusting the drug delivery constantly and consistently according to the patient's minute to minute requirements. The mobile phone would also constantly receive feedback from the infusion device thus giving the mobile phone full control over the entire system. The comprehensive information collected by the mobile phone could then be transmitted real time to the patient's and the neurologist's personal computer real time for long term storage and monitoring. The neurologist's role in such a device would just be to monitor the device periodically. Such automated systems could eliminate all possible human errors starting from the patient up to the neurologist. Additional information such as heart rate, body temperature, blood pressure, blood glucose, oxygen saturation, ECG when

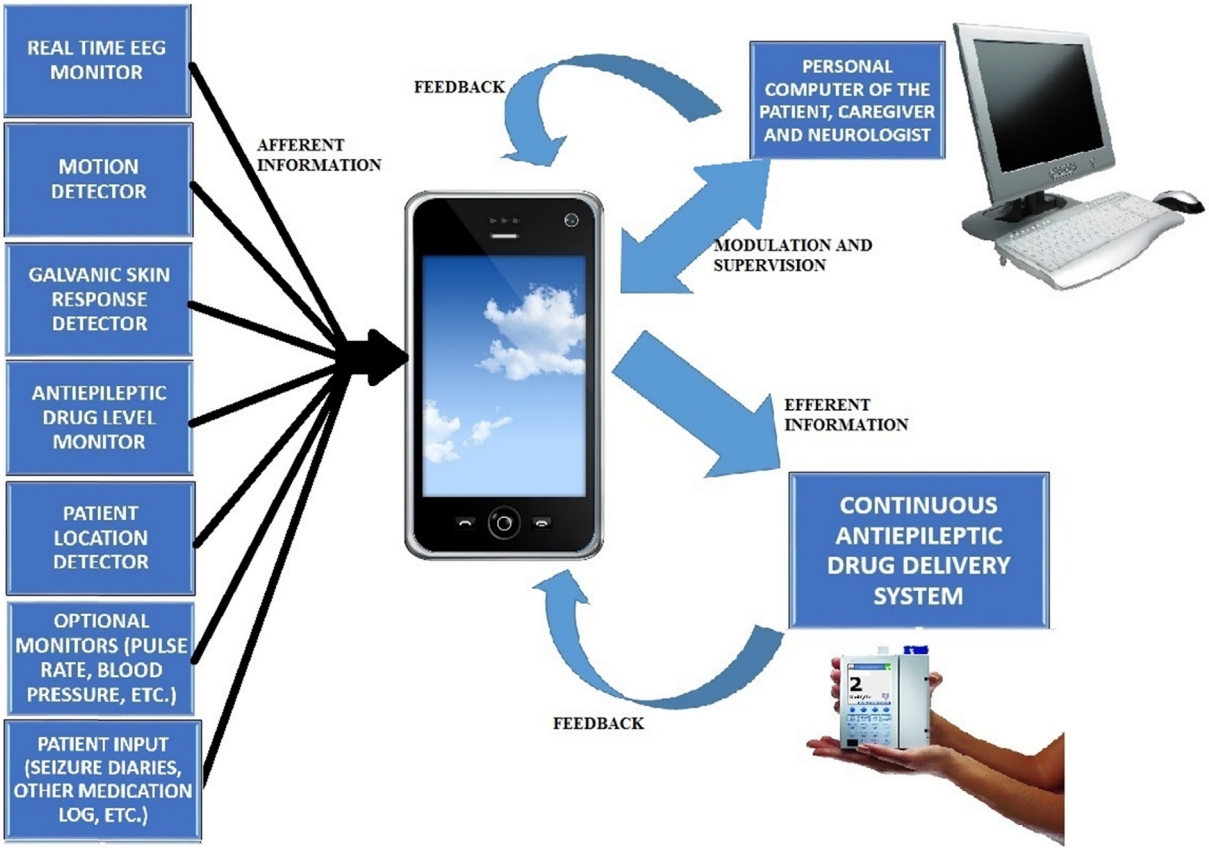

Fig. 9 – Comprehensive seizure detection, eeg monitoring, drug monitoring and drug delivery devices integrated to a mobile device.

monitored by separate units can be optional according to an individual's needs and when fed into the mobile phone could make this 'comprehensive' device even more comprehensive. The potential possibilities are thus limitless.

6. Conclusion

The advent of the mobile phone technology has influenced and revolutionised the IT sector and our day to day life tremendously. It is hard to imagine a day without mobile phone for an individual today. It's implications in the field of medicine is rapidly expanding and its potential applications in the field of epilepsy management and broadly in the field of neurology itself are innumerable. It is up to the medical and engineering personnel to collaborate and develop comprehensive devices for better patient care especially in the field of epileptology in the future.

Conflicts of interest

All authors have none to declare.

REFERENCES

1. Universitat Politècnica de Catalunya. Advances. In: *Medical Technology: What Does The Future Hold?*. *ScienceDaily*; 2009, June 16. Retrieved July 5, 2014 from www.sciencedaily.com/releases/2009/06/090616080133.htm.
2. McGill University Health Centre. McSleepy meets DaVinci: doctors conduct first-ever all-robotic surgery and anesthesia. *ScienceDaily*. October 2010;20. www.sciencedaily.com/releases/2010/10/101019171811.htm.
3. Hu Jim C, Gu Xiangmei, Lipsitz Stuart R, et al. Comparative effectiveness of minimally invasive vs open radical prostatectomy. *JAMA*. October 14, 2009;302.
4. Lum MJ, Rosen J, King H, et al. Telesurgery via Unmanned Aerial Vehicle (UAV) with a field deployable surgical robot. *Stud Health Technol Inf*. 2007;125:313–315.
5. Swartz Barbara E. The advantages of digital over analog recording techniques. *Electroencephalogr Clin Neurophysiol*. 1998;106:113–117. http://dx.doi.org/10.1016/S0013-4694(97)00113-2.
6. India's telecom subscriber base rises to 933 million. The Times of India. Retrieved 15 May 2014.
7. Hayes Daniel F, Markus Hugh S, Leslie R David, Topol Eric J. Personalized medicine: risk prediction, targeted therapies and mobile health technology. *BMC Med*. 2014;12:37.
8. Hodges Joseph C, Treadwell Janet, Malphrus Amy D, Tran Xuan G, Giardino Angelo P. Identification and Prevention of Antiepileptic Drug Noncompliance: The Collaborative Use of State-supplied Pharmaceutical Data. *Hindawi Publishing Corporation ISRN Pediatrics*; 2014. Article ID 734689 http://dx.doi.org/10.1155/2014/734689.
9. Meyer Sascha, Strittmatter Matthias. Autonomic changes with seizures correlate with postictal EEG suppression. *Neurology*. 2013;80:1538–1539. http://dx.doi.org/10.1212/01.wnl.0000429517.94343.7e.
10. Swenson NC, Picard RW, Poh Ming-Zher. A wearable sensor for unobtrusive, long-term assessment of electrodermal activity. *Biomed Eng IEEE Trans*. 2010;57:1243–1252. Copyright © 2010, IEEE.
11. Stopczynski Arkadiusz, Larsen Jakob Eg, Stahlhut Carsten, Petersen Michael Kai, Hansen Lars Kai. A smartphone interface for a wireless eeg headset with real-time 3d reconstruction;. *Affect Comput Intell Interact Lect Notes Comput Sci*. 2011;6975:317–318.
12. Fisher RS, Ho J. Potential new methods for antiepileptic drug delivery. *CNS Drugs*. 2002;16:579–593.
13. Fisher RS, Chen DK. New routes for delivery of anti-epileptic medications. *Acta Neurol Taiwan*. 2006 Dec;15:225–231.
14. Halliday AJ, Moulton SE, Wallace GG, Cook MJ. Novel methods of antiepileptic drug delivery – polymer-based implants. *Adv Drug Deliv Rev*. 2012 Jul;64:953–964. http://dx.doi.org/10.1016/j.addr.2012.04.004. Epub 2012 Apr 30.