New era of personalised epilepsy management

The trial and error approach to epilepsy treatment has not changed for over a century but machine learning and patient derived stem cells promise a personalised and more effective strategy, argue

Patrick Kwan and colleagues

Epilepsy affects 50 million people worldwide with no age, ethnic, or geographical boundary.[1] Patients have recurrent seizures that can lead to injuries, cognitive decline, psychosocial dysfunction, and even death. Epilepsy is caused by brain insults such as trauma, stroke, tumour, inflammation, and infection as well as systemic changes resulting from genomic variation. Patients with epilepsy have increased comorbidities, including cerebrovascular, neurocognitive, and psychiatric diseases.[2] Better epilepsy control will therefore improve overall brain health.

Uncertainty in treatment response is major problem

Numerous drugs are available to treat epilepsy as well as non-drug interventions such as resective surgery, neuromodulation, and dietary therapies. Yet the current standard of care still relies on a trial and error approach of sequential regimens of antiseizure medications. Although there are guidelines on drug selection based on broad seizure type (focal or generalised onset) many drugs have similar efficacy when analysed on a group basis.[3] For any given patient, it is impossible to predict which drug will be most effective and should be selected as the initial treatment. Nor are there surrogate biomarkers that can reliably predict treatment responses or risk of drug resistant epilepsy in the routine clinical setting. The upshot is that patients must simply wait and see whether their epilepsy will be controlled, usually defined as an absence of seizures for at least one year.[4] Despite an explosion of new drugs, with over 20 on the market, antiseizure medications fail to control seizures in one third of patients.[5]

Across much of the world most patients newly diagnosed with epilepsy are treated by primary care physicians (box 1). If seizure control is not achieved with initial treatment, patients are referred to a general neurologist who, if further drug treatments fail, then refers them to an epilepsy centre. This sequential care pathway means critical time is lost before patients who may be at high risk of drug resistant epilepsy can be assessed by epilepsy specialists.[6] Other treatment options, such as surgery, are widely considered a last resort. Sadly, the associated time delay means such treatments may be less effective.[7 8] The result is often years of reduced quality of life, lost productivity, and increased mortality.[9]

This predicament might be solved by a reliable method to find patterns linking treatment outcomes to a patient's personal characteristics. Patients with high risk of drug resistant epilepsy could be triaged early, expediting access to the precious resource of specialist care. Recent advances in artificial intelligence (AI) and stem cell research are raising hopes that personalised epilepsy management could soon be a viable alternative to this sequential treatment pathway (fig 1).

Medical artificial intelligence

Recent advances in machine learning, a subset of AI, offer novel ways to develop prediction models that are more accurate than traditional statistical modelling. Machine learning is being explored in epilepsy to forecast and detect seizures through recognition of electroencephalography (EEG) patterns. A recent study used 9571 routinely collected scalp EEG records to train a deep neural network that outperformed experts in detecting interictal epileptiform discharges.[11] Researchers have also used time series based algorithms (for example, the line length algorithm used in responsive neurostimulation systems[12]) to analyse controlled, continuously acquired, intracranial EEG signals to develop seizure warning systems.[13] If shown to be effective in large scale clinical trials, such systems could help patients pre-empt and reduce injury from seizures.

Recent studies have used drug dispensing databases to develop models to predict drug treatment responses.[14 15] Although these are large datasets, the models do not capture detailed information about the individual or the disease and therefore lack potentially important data on treatment outcomes. Medical records, on the other hand, include comprehensive clinical information on epilepsy management and are a fuller repository of factors potentially linked to treatment outcomes.

In the past five years a more advanced subfield of machine learning, called deep learning, has achieved impressive gains in the areas of image recognition, natural language processing, and speech. The superior performance of deep learning over traditional machine learning mainly arises from its depth of architecture and the capacity to scale massive amounts of data and continuously improve with more observations. Extended graphical models have shown superiority in modelling dynamic and complex graph structured data, such as clinical data. These models can unravel the hidden structure and reveal the complex links between clinical variables to derive predicted probabilities of the outcome of interest.

In medical AI, models have been shown to be capable of automatically discovering and learning from complicated "hidden (latent) spaces" by encoding multiple observed features to fewer representation variables that are optimised for predicting the outcome of interest.[16-19] For instance, graphical models recently identified the spatiotemporal evolution of epileptic seizures by leveraging spatial and temporal information in structural longitudinal data.[20]

KEY MESSAGES

- For more than a century the approach to epilepsy treatment has been trial and error because there is no reliable way to predict which medications will work
- Advances in machine learning promise more accurate models to predict treatment outcomes for individual patients
- Genome-wide screening and sophisticated disease models using patient derived stem cells may allow precision epilepsy treatment in future

Box 1: Current treatment practice

Jane is a 30 year old woman with newly diagnosed temporal lobe epilepsy. Her EEG appears normal but an MRI shows right hippocampal sclerosis, the likely source of her seizures. In line with guidelines,[10] Jane's general practitioner prescribes lamotrigine, one of the many drugs shown to be effective against focal seizures. Jane has more seizures and a few months later visits her GP who, appropriately, refers her to a general neurologist. Over the next few years Jane tries various drugs, some of which are stopped because of side effects, and is eventually maintained on three drugs. Despite this, ongoing seizures mean Jane cannot drive, loses her job, and becomes depressed. The neurologist refers her to an epilepsy centre to be evaluated for surgery.

Biomedical Bidirectional Encoder Representations from Transformers (BioBERT)[21] is the latest pretrained biomedical language representation model based on deep learning techniques and designed for biomedical text mining. BioBERT, released in early 2020, supports model training by facilitating use of unstructured data from many additional sources, such as electronic health records and clinical reports. This is combined with powerful deep learning graphical models, allowing researchers to include more granular and potentially useful information in the analysis of treatment outcomes, something not possible with traditional statistical analysis.

These AI advances raise the hope of robust models to predict drug treatment responses. A study at the Stanford Epilepsy Center is developing AI models to predict outcomes of antiseizure medication treatment from participants' seizure, genetic, physical, physiological, medication, and environmental data.[22] The ideal AI algorithm and input data to predict drug treatment responses are not yet known. Future studies should therefore explore more advanced and complex graphical AI models and use data from large, longitudinal epilepsy registries so that comprehensive information can be mined from patients' medical records. Those studies might enhance the models by applying natural language processing tools to extract unstructured data.

Although clinicians may be getting used to software being incorporated into their workflow, the "black box" nature of deep learning based AI systems could still hamper uptake. There have, however, been recent advances in the visualisation of AI based support of clinical decision making processes across multiple areas.[23] Determining the interoperability of models that visualise knowledge encoded within deep neural networks, and how this is affected by the data input, is also important for the development of novel treatment models.[24]

Genomics, stem cells, and precision treatment

Genome-wide screening of patients has identified a growing list of genes, single nucleotide gene variants (SNVs), and genome hotspots associated with epilepsy. Around 70% of epilepsy cases may be due to one or more genetic factors.[25 26] Even as examples emerge,[27 28] it remains unclear to what extent identification of pathogenic genetic variants will influence treatment decisions in clinical practice. To address that knowledge gap, a randomised controlled trial is investigating the clinical utility and cost effectiveness of whole genome sequencing in patients with refractory epilepsy.[29]

If genetic knowledge is to translate into better treatment it is critical to have a clearer understanding of the functional role of genetic variation. Researchers have traditionally studied this using animal and cellular disease models that insert the errant gene into an organism's DNA. Pathophysiological changes are then established by comparison with a control, or wildtype, state.

In epilepsy, disease modelling studies of SCN1A mutations (a gene responsible for most cases of Dravet syndrome[30]) have pinpointed the pathology as a reduction in the sodium ion channel function of inhibitory interneurons.[31] That finding has led to a reassessment of drug selection in Dravet syndrome, avoiding drugs that block sodium ion channels as they could further reduce interneuron function and aggravate seizures.[32]

In most cases, however, the pathogenicity of SNVs has not been established because of the limited scope of disease modelling studies. If precision medicine is to be widely adopted in epilepsy, patients identified as having a genetic variant must get expedited testing. The genetic variant should be investigated using in vitro models to assess its pathophysiological consequences and tailor testing and selection of drug treatment.

One promising disease model uses neurons derived from induced pluripotent stem cells (iPSCs) generated from the patient. iPSCs carry the patient's genetic information and can be grown

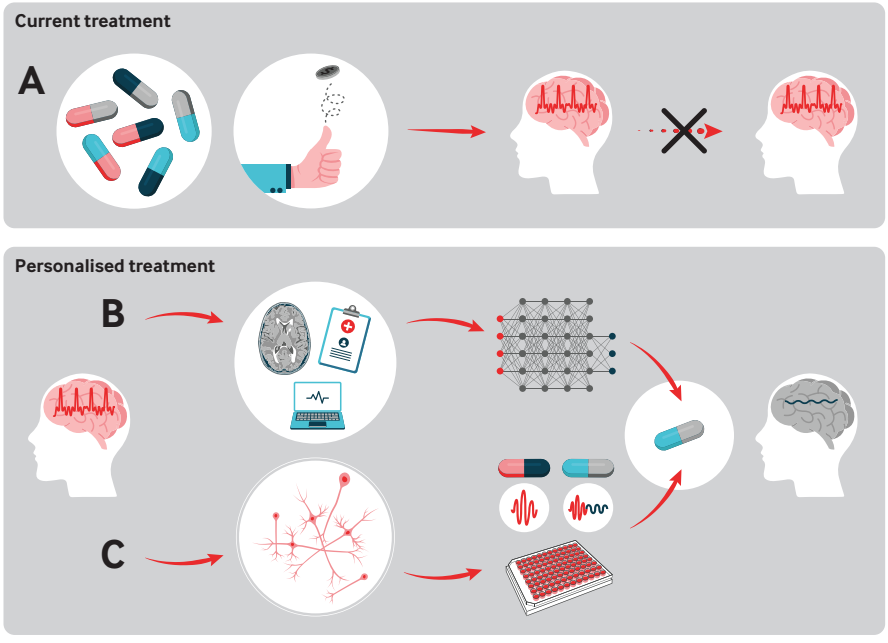

Fig 1 | Simplified conceptual view of how personalised treatment may be applied in epilepsy. Instead of the present trial and error approach (a) physicians could consult the decision supporting software for drug selection and identifying patients with high risk of drug resistance (b). Blood cells are obtained from patients to derive personalised disease models for drug screening to identify targeted and effective treatment (c)

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or "differentiated" into a variety of cell lineages, including multiple neural subtypes (fig 2). These patient derived neural models allow the study of genetic variation for a broad range of neural phenotypes, such as abnormal neural morphology or synaptic transmission, which is not possible with traditional models. The models have been used to identify the abnormal behaviour of neurones that carry highly pathogenic gene variants, as seen in early developmental encephalopathies.[33]

The advantages of iPSC based disease models include the ability to explore the combined effects of multiple SNVs in a single patient and cases where the genetic lesion is unknown.[34] There are, however, important hurdles to be overcome before these models can be used routinely in clinical decision making. More research is needed to show whether a hyperactive network phenotype, a hallmark of clinical epilepsy, can be reproduced in a dish. More study, too, is required to establish the relation between electrical activity measured in these in vitro models and epileptiform activity observed on EEG.

Current iPSC based neural models lack sufficient cellular complexity to establish seizure-like activity. Researchers are therefore turning to cerebral organoids that contain organised, multicellular tissue structures found in the brain.[35] More complex disease models will be essential to accurately model dysfunction in the broad range of cell types and brain regions that cause epilepsy in humans. In addition, multielectrode arrays, which record the coordinated interplay of networked neurons, have been used to detect EEG-like signatures from cultured cerebral organoids.[36]

Since iPSC based models can be grown indefinitely without risk to the patient, they will be important for high throughput screening of candidate compounds in patient specific conditions. The aim is to identify novel, targeted antiseizure medications. Indeed, these models have been successfully used for high throughput drug screening in other central nervous system diseases.[37] Such drug screening platforms could overcome our heavy reliance on traditional rodent models, which has hindered the development of antiseizure medications and helps explain why more than a third of patients with epilepsy lack effective treatment.

Future of personalised epilepsy management

If personalised epilepsy management is to become a reality technological advances must be coupled with improved health education and access to specialist care. The Australian Epilepsy Project (https://epilepsyproject.org.au) aims to build a network of centres to improve access for people living with epilepsy, especially in rural regions. It will recruit 8000 patients over five years to develop clinical decision support models by training AI algorithms on advanced imaging, neurocognitive functions, genetics, and other clinical features. The outcome prediction models will not only be of value to specialists but help general practitioners, who can use them to triage patients for early referral to epilepsy centres (box 2). Instead of the current trial and error approach physicians will consult decision support software that incorporates multimodal data for machine learning modelling. Personalised disease models derived from patients with drug resistant epilepsy will integrate clinical data for decision making and screen for novel, approved compounds as precision treatment. Fields such as oncology[38] have shown that combining in vitro models with clinical char-

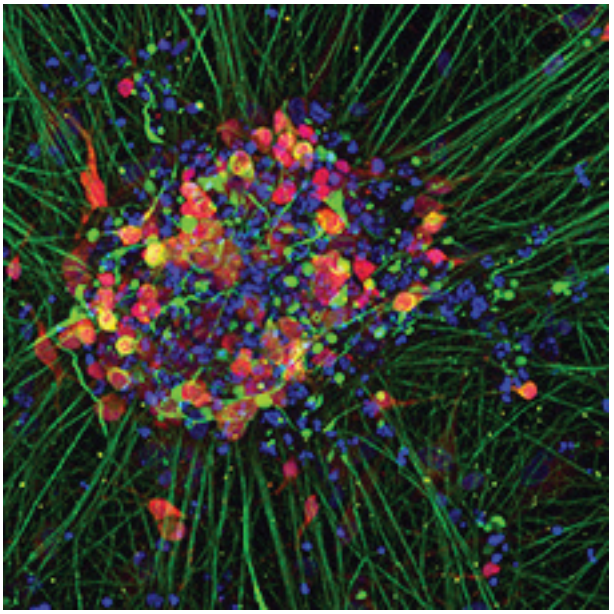

Fig 2 | "Epilepsy in a dish" models comprise human neurons derived from patient iPSCs. Here they grow as small clusters of neurones (red) and from which project long ranging axons (green). The nuclei of supporting astrocytes and senescent cells are shown in blue. These models will advance precision medicine and identification of new targeted drugs for epilepsy

Box 2: The near future

AI based clinical decision support models accurately predict the likely success of each antiseizure medication for an individual patient. The models are converted to software, approved by the US Food and Drug Administration and other regulatory authorities, under the category "software as a medical device." Used standalone or integrated into electronic medical record systems, the software improves performance using real world feedback. It identifies patients at high risk of drug resistant epilepsy and expedites early, targeted access to costly specialised care or surgical evaluation. The software proves cost effective and is used to prioritise patients for access to specialised epilepsy centres.

Jane's GP diagnoses epilepsy and enters Jane's data into the AI based treatment decision support software. The information includes seizure type and frequency, epilepsy risk factors, EEG and MRI results, medical history, and demographic and other relevant data. Within seconds, the software concludes there is an 80% chance Jane's epilepsy will not respond to the available antiseizure medications and recommends she is prioritised for specialised care. The GP promptly refers Jane to an epilepsy centre. She has a blood sample taken for screening using cerebral organoids against a library of compounds. The screening shows a drug currently used to treat another condition may be effective. Based on a favourable assessment of the risks and benefits, the drug is "repurposed" to treat Jane's epilepsy. Her seizures stop and her life is back on track.

acteristics can yield predictive models more powerful than those using either data type alone. Our hope is that a convergence of technologies could, within five to 10 years, make personalised epilepsy management a clinical reality.

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