PROGRESS IN MIND
Resource Center

EAN VIRTUAL 2021

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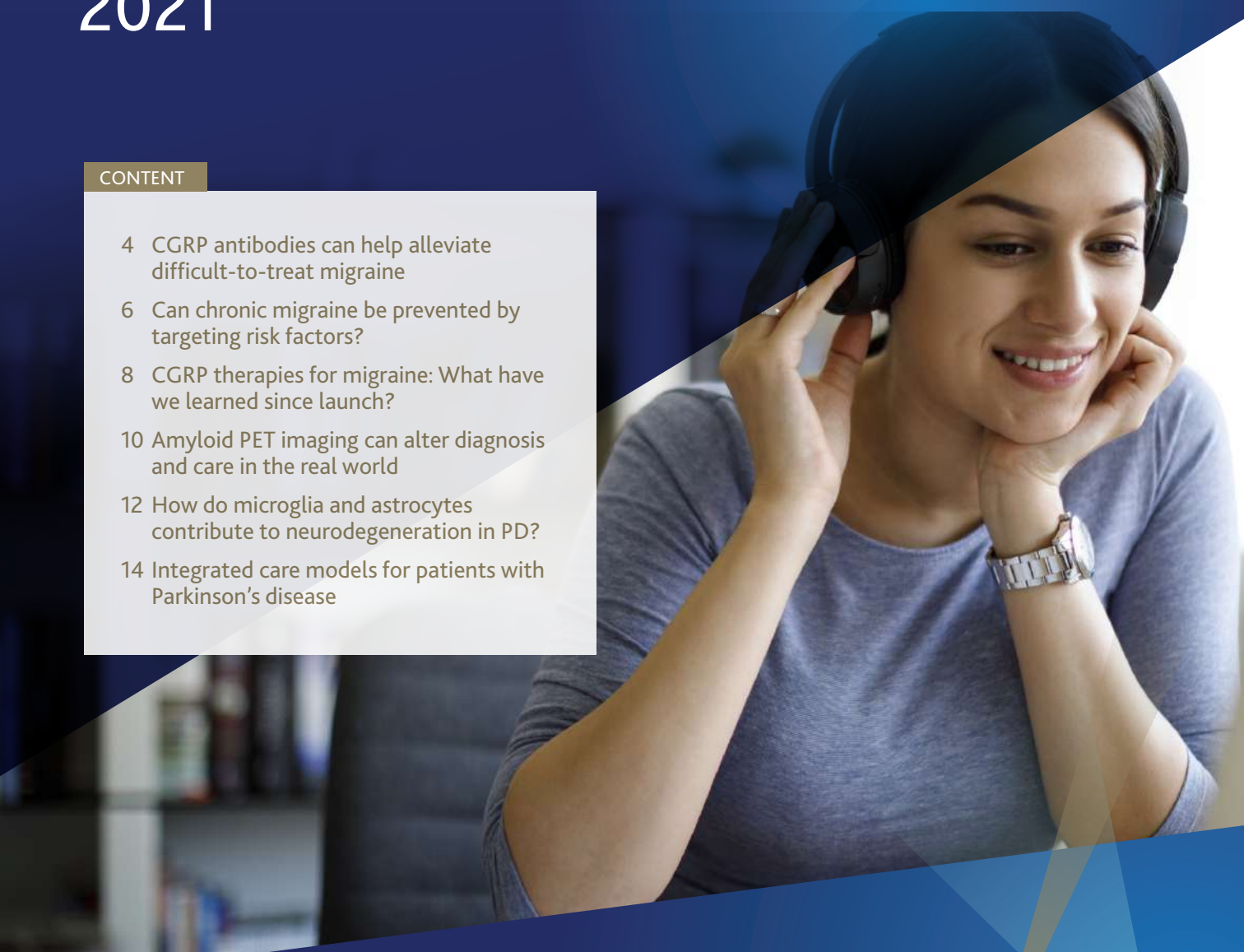

EAN VIRTUAL

7TH CONGRESS OF THE EUROPEAN ACADEMY OF NEUROLOGY 2021

Welcome to
Progress in Mind Resource Center

This magazine gives you a flavor of the content you will find in www.progress.im, a website brought to you by a dedicated team of medical and healthcare writers whose goal is to deliver the latest news, views and insights relating to a variety of topics within psychiatry and neurology. On this single platform, you can find a mix of face-to-face interviews, current views, webinars, insights from global and local opinion leaders. You can also enjoy timely reporting from international and national congresses to cover your educational needs. The Progress in Mind Resource Center brings you the newest trends and the latest discussions in your field.

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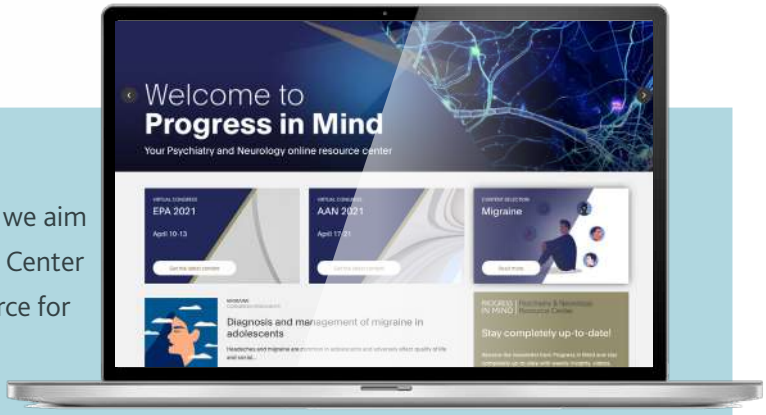
Articles and interviews in this publication have been written by journalists or medical experts on request by Lundbeck. The aim is primarily to focus on psychiatric disease and disease awareness in the congress reporting.

Our correspondent's highlights from the symposium are meant as a fair representation of the scientific content presented. The views and opinions expressed on this page do not necessarily reflect those of Lundbeck.



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MIGRAINE

CGRP antibodies can help alleviate difficult-to-treat migraine

Clinicians and researchers are continually expanding our understanding of disease mechanisms and addressing evolving and complex treatment challenges to improve the lives of people with migraine. During a satellite symposium held at #MTIS2020, clinical experts discussed complex migraine cases to identify recent progress in managing difficult-to-treat migraine.

Defining difficult-to-treat migraine

The European Headache Federation (EHF) recently defined two categories of resistant and refractory migraine to raise awareness of patients who suffer from difficult-to-treat migraine.[1] Complicated migraine can include chronic migraine, medication overuse (MO), migraine refractory to treatment, migraine with psychiatric or cardiovascular comorbidities, and older patients.

Older age imposes extra burden

Professor Christian Lampl, Headache Medical Centre, Linz, Austria described the additional complications associated with treating migraine that persists into older age. Migraine is the second commonest headache disorder in older patients – 1-year is prevalence approximately 10% in older adults2 – with a different phenotype (more often bilateral) and associated late-life migraine accompaniments: increase in neck pain and autonomic symptoms and a reduction in sensory symptoms, nausea and vomiting.[3] Patients aged >65 years with migraine also have an increased risk of depression compared with healthy controls.[4] And treatment of migraine in older patients is complicated by accumulation of multiple comorbidities, polypharmacy, and physiological changes that influence pharmacokinetics and pharmacodynamics.[3]

CGRP antibodies for difficult-to-treat migraine

Professor Tim Jürgens, University Medical Center Rostock, Germany summarized results of recent clinical trials of CGRP monoclonal antibodies (mAbs) in difficult-to-treat migraine. All CGRP mAbs have demonstrated efficacy in MO, and most have shown efficacy for migraine prevention in patients aged ≥60 years, those with psychiatric comorbidities, and patients with cardiovascular (CV) risk factors.

In older patients, CGRP mAbs result in reduction in monthly migraine and headache days (MMD/MHD) and are generally well tolerated.[5-7] In patients with psychiatric comorbidities, reductions in MMD and MHD may be achieved alongside improvement in depressive symptoms.[8,9] In migraine patients with CV risk factors, CGRP mAbs are not associated with any increase in CV adverse events versus placebo.[10,11] And in MO, CGRP mAbs result in a reduction in acute medication use and reversion to no medication overuse headache levels.[12,13]

> Migraine in older age is likely to become a far greater personal and public health issue over the next 40 years and management will be confounded by other health problems

Future research targets

Professor Anthony Dickenson, University College London, UK, recapped on the last 40 years of research into understanding the role of neuropeptides and the trigeminal vascular system in migraine, leading to identification of the role of CGRP and pituitary

adenylate-cyclase-activating polypeptide (PACAP) as triggers of migraine and the availability of anti-CGRP medications which have transformed the treatment landscape.[14]

Outstanding questions are the focus of ongoing research, which include unravelling the molecular mechanisms of attacks, and the role of mutations/polymorphisms, ion channels, inflammation, and vascular factors in migraine pathophysiology.[14]

> 40 years of research led to the anti-CGRP medications that have transformed the migraine treatment landscape

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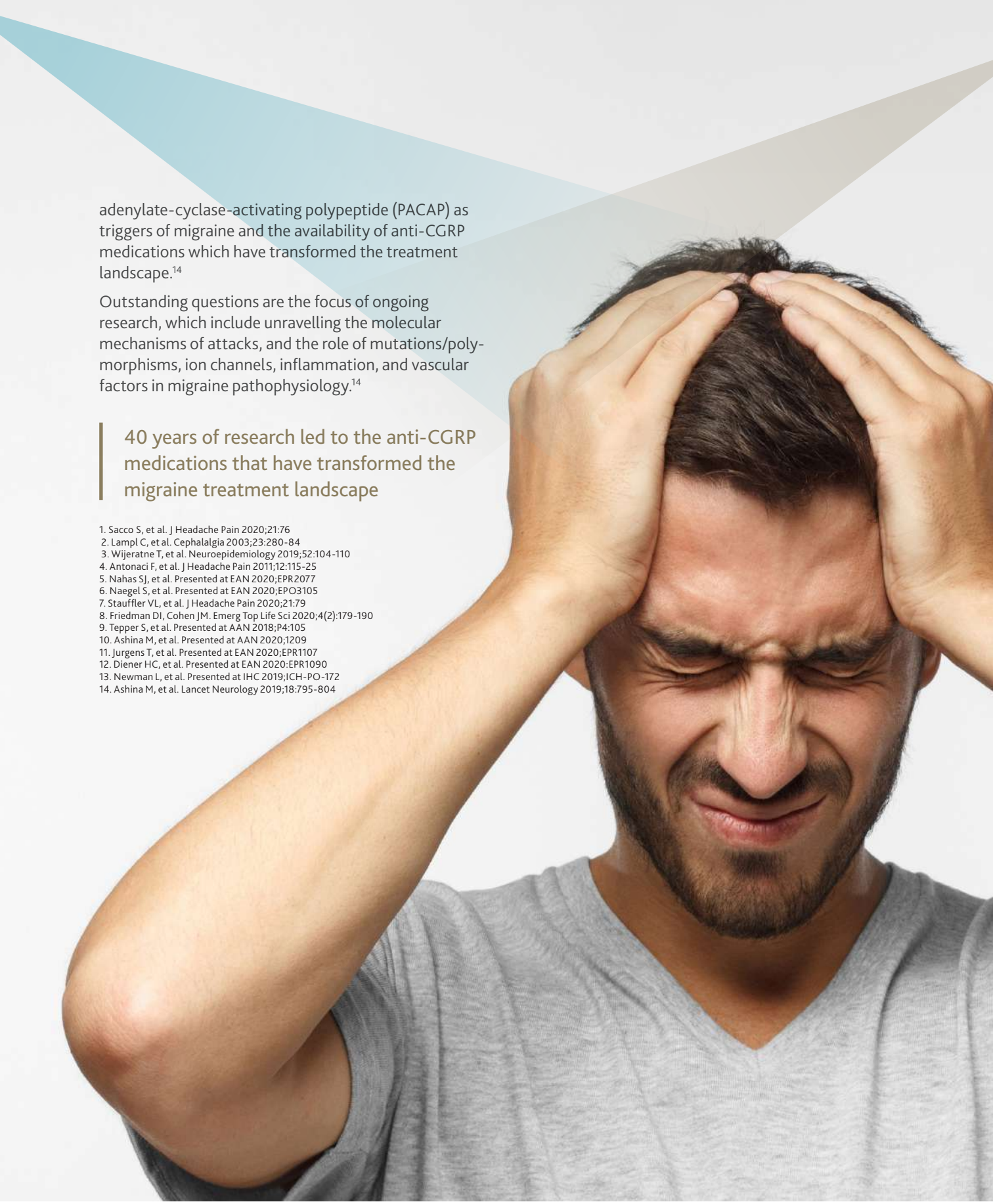

MIGRAINE

Can chronic migraine be prevented by targeting risk factors?

Many risk factors have been identified for predicting the transition from episodic to chronic migraine. Interventions to treat these risk factors have, however, not been studied, but are still worth considering and implementing for patients with episodic migraine, said Professor Richard Lipton, Albert Einstein College of Medicine, CT, at the Virtual Scottsdale Headache Symposium 2020.

Migraine is a common chronic disorder with episodic attacks, said Professor Richard Lipton, Albert Einstein College of Medicine, CT.

In the United States, the prevalence of migraine is 18% among women and 6% in men;[1] and every year, episodic migraine progresses to chronic migraine in 2.5% of patients,[2] he explained.

Many risk factors have been identified for predicting this transition[3–10] and treating them might therefore prevent progression. Although such interventions have not been studied, they are still worth considering and implementing, said Professor Lipton.

> Treating risk factors might prevent progression to chronic migraine

Important to address poor response to acute treatment and depression

Inadequate acute treatment efficacy is associated with an increased risk of new-onset chronic migraine, with rates of 1.9%, 2.7%, 4.4% and 6.8% over 1 year among those with maximal, moderate, poor, and very poor treatment efficacy, respectively.[11]

Improving acute treatment outcomes might therefore prevent new-onset chronic migraine, commented Professor Lipton. This also lowers the risk of medication overuse,[9] which is another risk factor.

Furthermore, barbiturates and opiates, which are pharmacologic treatment options for acute episodic migraine, are associated with an increased conversion rate to chronic migraine,[2] so alternative therapies are recommended to avoid this risk.

> Depression is a prognostic factor for migraine

Severity of depression also predicts increased risk for new-onset chronic migraine over the following year with OR=1.77 (95% CI 1.25–2.52) for moderate depression, OR=2.35 (95% CI 1.53–3.62) for moderately severe depression, and OR=2.53 (95% CI 1.52–4.21) for severe depression.[12]

Effective treatment of depression might therefore lower the risk for chronic migraine, said Professor Lipton.

> Efforts to address barriers to care are needed to improve outcomes

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Interventions to address other risk factors

Professor Lipton also enumerated the following risk factors for progression and the interventions that might prevent chronic migraine:

- attack frequency[3]—reduce frequency with pharmacologic and behavioral interventions
- obesity[3]—manage with weight loss, exercise and bariatric surgery
- comorbidities including depression and anxiety[4]—address with pharmacologic and behavioral therapies
- major life events[5]—implement biobehavioral techniques and exercise for associated stress
- snoring[6]—improve with weight loss and treatment of sleep apnea
- caffeine[7]—lower intake
- allodynia[8]—ensure early recognition and treatment
- Low socioeconomic status4 and head injury[10] are further risk factors.

Professor Lipton highlighted that among people with migraine in need of medical care, only 25% traverse the three steps needed—consultation, diagnosis, and treatment/medication use—to achieve minimally appropriate care.[13] Barriers to care also need to be addressed to improve outcomes, he concluded.

MIGRAINE

CGRP therapies for migraine: What have we learned since launch?

Today is a most exciting time in the migraine field given the plethora of new therapies introduced over the last two years, said Professor David Dodick, Mayo Clinic College of Medicine, USA when opening his Migraine Trust award lecture at #MTIS2020. He went on to outline key learnings on the transition of monoclonal antibodies targeting calcitonin gene-related peptide from randomised controlled trials to use in everyday clinical practice, bringing benefits to people with migraine worldwide.

Superior effectiveness in clinical practice

Professor Dodick reviewed the evidence emerging for real-world effectiveness gained since launch of this new class of therapeutics. Retrospective cohort studies conducted in Italy and the USA show that, in terms of efficacy, CGRP mAbs in everyday practice outperform the results from clinical trials.[4-6]

> This is the most exciting time in the migraine field given the plethora of new therapies introduced over the last two years

In an observational study of people with episodic or chronic migraine in the Abruzzo region of Italy (N=89), 70% of patients had a 50% decrease in monthly migraine days (MMD) within 3 months and after 6 months the median MMD decreased by 15 days from 19 to 4 days ($p<0.001$).[4] Patients also reported a reduction in consumption of acute analgesic medications, and reduction in depression and anxiety during 6 months of CGRP mAb therapy. Among people with MOH, over 70% reverted to non-MOH within 6 months.[4]

In a highly burdened patient population with chronic migraine (N=43), comorbidities (depression, anxiety, chronic pain, IBS) and multiple prior preventives use (mean 11 agents), the number of monthly headache days (MHD) decreased significantly from 24.8 to 18.3 days, and similarly MMD decreased from 19.1 to 10.7 days at 6 months following CGRP mAb therapy ($p<0.001$).[5]

> In terms of efficacy, CGRP antibodies in everyday practice outperform the results from clinical trials

Safety – benefits outweigh any drawbacks

Adverse events reported with CGRP mAb use in clinical practice appear to be more frequent and more diverse than those identified from clinical trials; however, the overall discontinuation rate due to adverse events is still quite low at around 8-12% of treated patients. The most frequent side effects reported included constipation, injection site reaction, fatigue, worsening headache, and dizziness.4-6 Allergic reaction occurs in a minority of patients (1-3%).[4-6]

Nonetheless, for many patients the advantages of new preventive treatments overshadow any side effects. A retrospective cohort study conducted at the Harvard Medical School, found that among 241 patients who had received CGRP mAb therapy, 70% of patients felt that the benefits of treatment outweighed any drawbacks and 63% planned to continue use of CGRP antibodies.[6]

70%

of migraine patients felt that the benefits of new CGRP antibody therapy outweighed any drawbacks

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ALZHEIMER'S DISEASE

Amyloid PET imaging can alter diagnosis and care in the real world

Access to amyloid PET changes the diagnosis and care of many patients in whom the diagnosis of Alzheimer's Disease is uncertain. Updated results from the large IDEAS study showing the clinical utility of amyloid PET also support a clear link between air pollution and brain amyloid deposits.

Seventy-two percent of people who turned out to be amyloid negative on PET scan had been given a pre-PET diagnosis of Alzheimer's Dementia and would have been managed accordingly. This striking finding was reported at an update on a major US study given at ADPD 2021 Virtual by Gil Rabinovici (University of California, San Francisco).

The study demonstrates that amyloid PET scans have real-world clinical utility and can improve patient care, as well as having transformed dementia research, said Professor Rabinovici.

> Amyloid PET changed at least one aspect of management in 60% of diagnostically uncertain cases

IDEAS can change the world

In the Imaging Dementia – Evidence for Amyloid Scanning (IDEAS) Study, more than 18,000 people diagnosed within the past two years as having objective mild cognitive impairment (MCI) or dementia had an amyloid PET scan with one of three FDA-approved amyloid-β tracers.

Those enrolled across almost six hundred dementia practices had a diagnosis that was uncertain following comprehensive evaluation by a dementia specialist which included CT/MRI.

Of those with an MCI diagnosis, 55% turned out to be Aβ positive on PET, while this was true of 70% of those with a dementia diagnosis. In 25% of cases overall, an AD diagnosis pre-PET was changed to a non-AD diagnosis following the scan. And in 11% of cases a non-AD diagnosis was changed to AD.

Management change follows change in diagnosis

Overall, having amyloid PET changed management in more than 60% of cases. This composite outcome included change in AD medications (cholinesterase inhibitor or memantine), change in relevant non-AD medications (such as those used to treat cognition or other neurologic disorders), and change in counseling

about safety and planning for the future, such as independent living.

The study, which was directed by the Alzheimer's Association, compared the care plan decided on when it was assumed there would be no access to amyloid PET with the care implemented 90 days after the results of the scan were made available.

PET led to a change in diagnosis in a third of cases

Air pollution linked to PET amyloid pathology

The IDEAS data have shown another real-world effect: living in areas polluted by high concentrations of fine particulate matter (PM2.5) is associated with a significantly higher likelihood of being positive on an amyloid PET scan.[1]

This association is dose dependent and statistically significant after adjusting for demographic, lifestyle, and socioeconomic factors. IDEAS researchers also looked at ground-level concentrations of ozone, but found no influence on amyloid PET scan positivity.

Following the success of IDEAS, a recently-launched study will focus on amyloid PET imaging in populations under-represented in the initial trial. Provision of a biorepository for DNA and plasma is part of the new initiative.

More IDEAS to follow

It is hoped that by the end of 2021 data and images from the original IDEAS study will be made available to the research community through the Global Alzheimer's Association Interactive Network (GAINN.

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PARKINSON'S DISEASE

How do microglia and astrocytes contribute to neurodegeneration in PD?

Immune responses are involved in the pathophysiology of Parkinson's disease. Supporting evidence for these responses and the emerging roles of microglia and astrocytes was presented by experts at MDS Virtual Congress 2020.

Immune responses play a role in the pathophysiology of Parkinson's disease (PD),[1] said Professor David Sulzer, New York, NY. Evidence for this role has been provided by a number of studies:

Microglia are activated by extracellular neuromelanin

- leucine-rich repeat kinase 2 (LRRK2) regulates immune cell responses in the brain and LRRK2 mutation is a risk for PD2
- genome-wide association studies suggest the involvement of antigen-presenting cells3 such as microglia
- microglia are activated by extracellular neuromelanin leading to the production of pro-inflammatory factors and neurodegeneration4
- neuronal major histocompatibility complex class I (MHC-I) can trigger an antigenic response, and catecholamine neurons may be susceptible to T-cell-mediated cytotoxic attack5
- α-synuclein-specific T cell responses are highest shortly after a diagnosis of motor PD
- α-synuclein-specific T cell responses have been detected before a diagnosis of motor PD and are highest shortly after the diagnosis, but then decline6
- increased T-helper cell 17 (Th17) frequencies have been found in the blood of patients with PD, increased numbers of T cells have been detected in post-mortem PD brain, and co-culture of induced pluripotent stem cell (iPSC)-derived PD midbrain neurons with T cells or the addition of interleukin-17 (IL-17) leads to increased neuronal death driven by upregulation of the IL-17 receptor (IL-17R) and NFkB activation7usual in rates of therapy discontinuation, involvement in school or work, and severity of both positive and negative symptoms.[4]

Research carried out by Professor Antonella Consiglio, Barcelona, Spain, and her colleagues supports the role of astrocytes in PD pathophysiology.

α-synuclein accumulates in control cells co-cultured with PD astrocytes

She described the studies of iPSC-derived astrocytes and neurons from familial mutant LRRK2 patients with PD and healthy individuals that demonstrated:

- neurodegeneration and abnormal astrocyte-derived α-synuclein accumulation in control ventral midbrain dopaminergic neurons (vmDAns) co-cultured with PD astrocytes
- disease-related phenotypes in PD vmDAns were partially prevented by control astrocytes
- dysfunctional chaperone-mediated autophagy (CMA), impaired macroautophagy, and progressive α-synuclein accumulation in PD astrocytes
- clearance of α-synuclein accumulation by chemical enhancement of CMA protected PD astrocytes and vmDAns8neurons with T cells or the addition of interleukin-17 (IL-17) leads to increased neuronal death driven by upregulation of the IL-17 receptor (IL-17R) and NFkB activation7usual in rates of therapy discontinuation, involvement in school or work, and severity of both positive and negative symptoms.[4]

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PARKINSON'S DISEASE

Integrated care models for patients with Parkinson's disease

Integrated care is critical for people who have Parkinson's disease for optimal management of their complex multisystem challenges, said Professor Terry Ellis, Boston, MA, who introduced a scientific session at MDS Virtual Congress 2020 on innovative care models. Three experts then described a variety of evidence-based and innovative integrated care models for optimal and responsive management of patients throughout the course of Parkinson's disease.

The multisystem nature of Parkinson's disease (PD) results in a wide variety of motor, autonomic, behavioral, sensory, mood, cognitive, sleep, and other symptoms.[1] Effective management patients with PD therefore involves multiple disciplines and team members, said Professor Jennifer Goldman, Chicago, IL.

An interdisciplinary care model responds to patient needs

An interdisciplinary care model has been found to provide optimal PD management, she said. It's patient-centered approach is combined with close communication and integration of knowledge by the professionals from different disciplines throughout the course of a patient's illness to respond to needs defined by the patient.[2,3]

In contrast, in a multidisciplinary care model, professionals from different disciplines work together in parallel but do not integrate their knowledge and the goals might not be defined by the patient.[2,3]

Integrated care models

Integrated care models optimise the management of PD

Existing integrated care models are heterogenous, including in setting, scope, and team members,[2] but have been shown improve outcomes and quality of life, for example:

- day clinics improved motor and non-motor scores and quality of life[4]
- intensive rehabilitation improved quality of life5
- tiered screening models led to early involvement in rehabilitation programs[6]
- home-based care for patients with advanced PD was associated with high satisfaction and retention in the program[7]

Among the most important principles of a good interdisciplinary team are respect, good communication, and positive leadership and management.[8]

Innovative models of integrated care

Innovative models of integrated care involving telemedicine and for providing palliative care also improve outcomes for patients with PD.

Interdisciplinary telemedicine is as effective as face-to-face consultation

Interdisciplinary telemedicine presents many opportunities for improving healthcare for patients with PD,[9] including access to patients in remote areas or who are housebound, said Dr Mark Guttman, of Toronto, Canada, who has used telemedicine in his management of patients with PD over the past 19 years.

He described a randomized controlled trial (RCT) of usual care compared with usual care including virtual visits. Telemedicine consultations were found to be feasible and as effective as face-to-face consultations.[10]

Outpatient integrated palliative care improves patient outcomes

Professor Maya Katz, San Francisco, CA, advocated an integrated outpatient palliative care model for PD, and described an RCT of outpatient integrated palliative care compared with standard care.

The integrated outpatient palliative care model produced statistically significant improvements in:

- quality of life
- nonmotor symptom burden
- motor symptom severity
- caregiver burden at 12 months[11]

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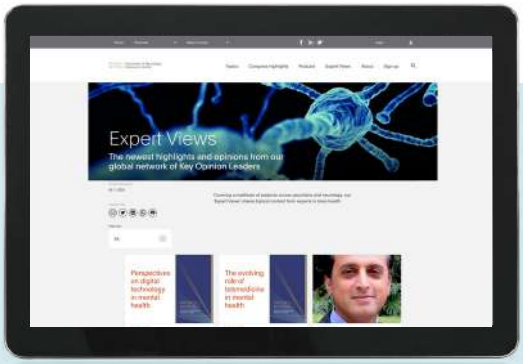

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