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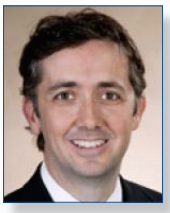
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Neurotherapeutics: Recent Developments

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Diseases of the nervous system often have devastating outcomes. Unfortunately, treatments for neurological disorders, which primarily tend to be progressive, are very limited. The last two decades have seen game-changing clinical developments in neuroimmunology and neuro-intervention. In this section, we will review some recent progress in four different subspecialties of neurology.

Multiple Sclerosis (MS)

Treatment of MS, that is, slowing of disease progression, has evolved from no evidence-based treatments prior to 1994 to 14 different FDA-approved disease-modifying agents in 2017. As the treatments become more effective, the threshold for tolerating disease activity has decreased. Most MS specialists now aim for NEDA (No evidence of disease activity based on MRI, relapse and disability progression). The treatment choices have expanded and offer a more aggressive approach but with increasing risk of serious adverse events. Progressive Multifocal Leukoencephalopathy (PML) has now been associated with several of the disease-modifying agents. Wong et al. review the current options in the treatment of MS.

Stroke

The acute management of cerebrovascular disease has undergone a dramatic change in the last few years. Several studies have validated the use of aggressive and early intra-arterial intervention and in selected cases expanded the window of intervention for up to 24 hours. There is also increasing evidence supporting a more aggressive approach towards detecting atrial fibrillation and secondary prevention. Mac Grory et al. review the latest advances in stroke management

Parkinson's Disease (PD)

PD continues to be a frustrating and difficult to manage neuro-degenerative disorder. Several new agents including different formulations of Levodopa and dopamine now offer additional options for optimizing care in these patients. Device-based treatments including Deep Brain Stimulation (DBS) and Levodopa Carbidopa Intestinal Gel (LGIC) are increasingly used in a select group of patients. D'Abreu reviews the latest in the management of PD. Unfortunately, no intervention has been shown to slow progression.

Epilepsy

Uncontrolled epilepsy carries significant risk of morbidity and mortality. Up to 30% of patients continue to have seizures despite appropriate treatment with multiple agents. These patients benefit from a comprehensive evaluation at an epilepsy center with experience in epilepsy surgery. Bayer et al. review the surgical options for management of intractable epilepsy.

Guest Editor

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Moving Towards a Cure for MS: Increased Immunosuppression and Striving for No Evidence of Disease Activity (NEDA)

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ABSTRACT

Multiple sclerosis (MS) is a chronic central nervous system demyelinating disease. The cause is unknown, but likely results from a combination of genetic predisposition and environmental exposures leading to autoimmune destruction of the brain and spinal cord. The most common phenotype of MS is relapsing-remitting (RRMS), characterized by episodes of neurological symptoms, typically lasting days to weeks, followed by symptom remission. After years of disease, the majority of RRMS cases transform into secondary progressive MS (SPMS), characterized by slowly worsening symptoms and progressive neurological disability, which may or may not be also accompanied by superimposed relapses. A third distinct phenotype, primary progressive MS (PPMS) is characterized by slowly worsening neurological symptoms and disability from disease onset, without clinical relapses.[1]

The first disease-modifying agent was approved by the FDA in 1993. There are now 14 FDA-approved disease-modifying therapies (DMTs) with almost all agents indicated for relapsing forms of MS. The medical management of multiple sclerosis has changed dramatically over the past decade as the number of available DMTs has increased (**See Table 1**).

Most of the newer agents have been shown to decrease clinical relapse rates to a greater degree than the older agents. These DMTs frequently also decrease the rate of disability progression in MS. With the increased immunosuppression of the newer therapies comes the potential for more serious side effects. Balancing efficacy with potential adverse events is a primary consideration of patients and clinicians treating MS today. The potential for near complete control of the disease is becoming a reality in select cases, and a new goal of "no evidence of disease activity" (NEDA) may be supplanting the previous aim of relapse rate reduction.

KEYWORDS: multiple sclerosis, NEDA, disease-modifying therapy, PML

ESCALATION VS. INDUCTION THERAPY

Early in the disease course, multiple sclerosis is characterized by periods of inflammation associated with demyelination and axonal injury. However, as the disease reaches a later progressive phase, inflammation and relapses become less prominent and neurodegeneration becomes the more defining feature of the illness. It has been proposed that aggressive treatment early in the disease course may have a greater effect on morbidity in multiple sclerosis because it is during this period that DMTs have the greatest opportunity to reduce inflammation. Two strategies used in selecting the best DMT to treat an individual MS patient are "escalation" and "induction" therapy.[2] An escalation approach has been widely utilized in the treatment of multiple sclerosis since the 1990s. This entails starting a patient on a first-line agent (typically glatiramer acetate or interferon-beta) and transitioning to a second-line agent only in the event of disease progression while on therapy. This is a reasonable strategy, as a patient may be well controlled on an agent with a long safety profile history. However, this approach does not take into consideration how early or late a patient is in their disease course or the degree of initial clinical or radiographic activity. Ultimately, the majority of patients starting treatment with glatiramer acetate or interferon-beta will continue to show evidence of disease activity. If there truly is a critical period early in the disease course where DMTs can provide the greatest impact, an aggressive approach may instead be warranted. This practice is analogous to induction chemotherapy for some cancers. Induction therapy is the alternative strategy where drugs with the highest efficacy are used for a defined period of time as an initial treatment despite their increased risk of serious side effects. Using an induction strategy to control inflammatory disease activity early in the course of MS, may ultimately decrease long-term disability.[2]

FIRST-LINE AGENTS

Glatiramer acetate and several interferon-beta preparations (**See Table 1**) are frequently considered first-line agents. Each of these self-injectable agents reduces relapse rates in relapsing MS by modest amounts (approximately 30–35% relapse rate reduction), but their effectiveness in preventing long-term disability progression is limited.[3]

The three oral agents approved for relapsing MS represent an advance in the treatment of the disease by reducing relapse

Table 1. Disease-modifying agents for multiple sclerosis

Drug	Brand name	First FDA-approved	Dosing and administration	Indication
Interferon-beta 1b	Betaseron, Extavia	1993	0.25mg SC every other day	Relapsing MS
Interferon-beta 1a IM	Avonex	1996	30mcg IM weekly	Relapsing MS
Glatiramer acetate	Copaxone	1996	20mg SC daily or 40mg SC three times a week	Relapsing MS
Mitoxantrone	Novantrone	2000	12mg/m2 IV every 3 months to lifetime max 140mg/m2	Relapsing MS and SPMS
Interferon-beta 1a SC	Rebif	2001	22-44mcg SC three times a week	Relapsing MS
Natalizumab	Tysabri	2004	300mg IV every 28days	Relapsing MS
Fingolimod	Gilenya	2010	0.5mg PO daily	Relapsing MS
Teriflunomide	Aubagio	2012	7-14mg PO daily	Relapsing MS
Dimethyl fumarate	Tecfidera	2013	240mg PO twice a day (after initial titration)	Relapsing MS
Peginterferon-beta 1a	Plegridy	2014	125mcg SC every other week	Relapsing MS
Alemtuzumab	Lemtrada	2014	12mg IV daily x5 days, then x3 days one year later	Relapsing MS
Daclizumab	Zinbryta	2016	150mg SC monthly	Relapsing MS
Ocrelizumab	Ocrevus	2017	600mg IV every 6months (with first dose split)	Relapsing MS and PPMS

rates to a greater degree when compared to the self-injectable agents, and in some cases showing decreased rates of disability progression.[3] Fingolimod and dimethyl fumarate both reduce relapse rates vs. placebo by approximately 50%.[4,5] Fingolimod also reduces relapse rates compared to an active comparator, intramuscular interferon beta-1a.[6] Teriflunomide reduces relapse rates by approximately 30% in relapsing MS and decreases the risk of sustained disability progression compared to placebo by ~26% over a two year period.[7]

Despite the improvements in efficacy with the oral agents, there are still many patients who experience clinical relapses, new MRI disease activity, and disability progression on these medications. Unfortunately, clinicians' ability to predict from disease onset which patients will fail to respond to the first-line injectable or oral agents is limited.

MONOCLONAL ANTIBODIES: MORE EFFICACIOUS, BUT GREATER RISK

To justify the use of agents with increased serious side effects, the disease severity may be considered. Some patients with multiple sclerosis have a rapidly progressive course and respond poorly to first-line agents. In this population, the risk of serious side effects from a second-line agent may be acceptable. Using a Canadian database containing 5891 patients with adult-onset MS, an attempt was made to define aggressive multiple sclerosis (AMS). The three definitions proposed were: (1) Expanded Disability Status Scale (EDSS) 6 or greater within 5 years of MS symptom onset, (2) EDSS 6 or greater by age 40, or (3) secondary progressive course within 3 years of a relapsing-onset course. Depending on the definition, between 4–14% of patients were characterized as having aggressive multiple sclerosis. There was a higher likelihood of aggressive MS in patients who were male, older at symptom onset, or presented with PPMS.[8]

An aggressive treatment approach could also be considered to achieve a disease activity free status in multiple sclerosis. The term "no evidence of disease activity" (NEDA) has emerged to describe this disease activity-free state.[9] More specifically, NEDA-3 has been defined as: (1) absence of relapses, (2) absence of focal MRI activity, and (3) absence of confirmed disability progression. While NEDA-3 captures inflammatory disease activity well, it may not fully account for the neurodegenerative component of MS. Thus another more stringent definition was developed. NEDA-4 includes the criteria included in NEDA-3, but also requires an annualized rate of brain volume loss of less than 0.4%.[10] Since brain volume loss has been shown to correlate with disability progression and cognitive decline, this definition may more accurately reflect a complete absence of disease activity. However, other researchers have noted that NEDA criteria do not fully capture disability related to MS, neglecting some cognitive measures, visual function, fatigue, and pain.[11,12]

Natalizumab was first approved by the FDA for the treatment of relapsing forms of MS in 2004. The medication is a humanized monoclonal antibody which binds to the α_4 subunit of $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins on the surface of lymphocytes. Binding to these integrins blocks lymphocytes' ability to interact with endothelial cell receptors (VCAM-1 and mucosal addressin-cell adhesion molecule 1) and prevents lymphocyte migration into the central nervous system. In clinical trials, natalizumab reduced clinical relapses (67% relapse-free at two years), new MRI disease activity (97% free of gadolinium enhancing lesions at two years), and disability progression (no EDSS disability progression in 29% compared to 17% of placebo).[13] The number of patients who met all the criteria satisfying NEDA-3 was not included in the final analysis of the study; however, a smaller Italian study of 152 patients with RRMS treated with natalizumab demonstrated that 34% of patients were able to maintain NEDA-3 status after 7 years of follow-up.[14]

Alemtuzumab, another intravenous infusion agent, was approved for use in the treatment of relapsing forms of MS in November 2014. Alemtuzumab is a humanized anti-CD52 monoclonal antibody which binds to the CD52 receptor on B and T lymphocytes causing a long-lasting depletion of lymphocytes. Alemtuzumab is given as an infusion over 5 days initially, repeated once for a cycle of three more days after one year. Most patients do not require further treatment for a period of five or more years. Alemtuzumab is perhaps the only true induction agent for the treatment of relapsing forms of MS. Following depletion, there is a subsequent slow repopulation of these cells. In clinical trials compared to subcutaneous interferon-beta 1a, alemtuzumab was superior in achieving an endpoint equivalent to NEDA-3 (referred to as "freedom from disease activity" in the study). 39% (139/360) of patients in the alemtuzumab arm maintained freedom from clinical or radiographic disease at 24 months compared to 27% of patients in the interferon beta 1a group. Furthermore, patients treated with alemtuzumab had less brain atrophy on MRI.[15]

The newest disease modifying agent, Ocrelizumab, was approved by the FDA in March, 2017 for both relapsing and primary progressive forms of MS. Ocrelizumab is a humanized monoclonal antibody that targets the CD20+ receptor found on pre-B cells, mature B cells, and memory B cells. This receptor is not present on stem cells or plasma cells. Thus the medication should preserve existing humoral immunity and potential for B cell reconstitution. The mechanism is identical to rituximab and only differs in that ocrelizumab is a humanized antibody rather than a chimeric antibody. In clinical trials of relapsing MS, ocrelizumab patients achieved NEDA-3 approximately 47% of the time, compared to approximately 27% in subcutaneous interferon-beta 1a.[16] The rate of brain volume loss in the ocrelizumab group compared with the subcutaneous interferon-beta 1a group was also decreased to a statistically significant degree in one study.

Ocrelizumab has also been shown to be effective in primary progressive MS. Although NEDA does not apply to PPMS and was not a secondary end point in this trial, the ocrelizumab patients had statistically significant better outcomes in disability progression (~25% relative risk reduction), volume of T2 lesions, and mean percentage change in brain volume when compared to placebo.[17] Based on this clinical trial, ocrelizumab became the first FDA-approved agent for the treatment of PPMS.

The mainstay of relapse treatment continues to be intravenous high-dose methylprednisolone. Acthar Gel (repository corticotropin injection) is used in rare cases where IVSM is not tolerated.

AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION

While modern disease modifying agents have demonstrated improved efficacy in minimizing disease progression in RRMS, autologous hematopoietic stem cell transplantation (AHSCT) for the treatment of MS, which can be considered the ultimate in induction therapies for MS, has also shown encouraging results. AHSCT for MS patients began in 1995 and by 2008 approximately 400 cases had been performed worldwide.[18] Although protocols from early transplantations varied greatly, even initial data showed a slowing of disease progression in a majority of patients following treatment. However, the procedure carries significant risk and transplant-related mortality was initially as high as 7.3%.

The protocol for AHSCT varies at each institution, but in general involves four main steps. First, hematopoietic stem cells are mobilized, typically using granulocyte colony stimulating factor. Then hematopoietic stem cells are collected in the patient's circulating blood. The patient's remaining immune cells are then eradicated via a "conditioning" regimen using one or several chemotherapeutic agents, and lastly the previously harvested stem cells are reintroduced to the patient.[18]

AHSCT has demonstrated NEDA status rates of 78–83% at 2 years and 60–68% after 5 years.[19]

ADVERSE EFFECTS AND MINIMIZING RISK

Because NEDA is a new concept in the MS treatment field, specific NEDA rates of the older agents are not readily available. In longitudinal follow-up studies for the older agents, and in the clinical trials for the newer agents, NEDA status rates between 13–46% have been reported after two years of treatment. Direct comparison of NEDA status rates is impossible due to variations in the study populations.

Decisions about disease-modifying therapy must be made with consideration given to risks and side effects as well as efficacy. There are few serious side effects from the older self-injectable agents, but with newer oral and infusible agents, treating neurologists must monitor for specific side effects (**See Table 2**) including hepatic dysfunction, cardiac arrhythmia, and ocular disorders.

With the increased immunosuppression of the newer highly effective agents, there is increased risk of possible serious infections, secondary autoimmunity, and malignancy. One such serious infection is progressive multifocal leukoencephalopathy (PML), which is a rare brain infection that can be fatal. PML is associated with several of the DMTs used for MS, and in the highest risk patients may occur at a rate of 13/1000 individuals. Therefore, carefully selecting the appropriate DMT for each patient is critical.

Despite the increasing number of medications, the cost of each of these drugs remains prohibitively high for many patients. On average, treatment with one of these agents costs $55,000/year and decision-making often requires consideration of insurance coverage limitations.

CONCLUSIONS

As newer therapies are used more frequently as the initial treatment in MS, and therapies are modified and refined to minimize side effects, there will likely be improved long-term outcomes and increasing rates of NEDA. The goals for

an individual patient starting treatment for MS today are shifting from reducing relapses to completely controlling the disease clinically and radiographically. Reducing disability in the long-term and decreasing morbidity of the disease over many years is becoming a reality. Although none of the treatments discussed here is a cure for MS, the field is increasingly moving toward that goal as patients and providers become less accepting of new symptoms, signs, or MRI changes.

Table 2. Common and serious potential side effects of the disease-modifying agents

Drug	Common side effects	Serious potential side effects
Interferon-beta	Post-injection flu-like symptoms Liver function abnormalities Depression	Rare
Glatiramer acetate	Injection site reaction (skin irritation)	None
Mitoxantrone	Few	Heart failure (0.4%) Hematological malignancy (0.8%)
Natalizumab	Few	PML JCV + patients (1/1000 patients) JCV – patients (extremely rare)
Fingolimod	Few	Macular edema (0.1%) Heart block (0.1%) PML (extremely rare)
Teriflunomide	Mild alopecia	Hepatic dysfunction (uncommon)
Dimethyl fumarate	Gastrointestinal upset, Abdominal cramping Flushing	PML (extremely rare)
Peginterferon-beta 1a	Post-injection flu-like symptoms Injection site reaction Depression Liver function abnormalities	Rare
Alemtuzumab	Infusion reaction	Immune thrombocytopenic purpura (ITP) (1%) Autoimmune thyroid disease (30%) Serious infections (uncommon) Glomerular disease (0.3%)
Daclizumab	skin rash	hepatic dysfunction (rare)
Ocrelizumab	Infusion reaction	Breast cancer? (unclear evidence)

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Updates in Stroke Treatment

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ABSTRACT

In this article, we discuss major advances in the treatment and prevention of ischemic stroke that have taken placed in the past 3 years. The most important advance in acute stroke treatment is the validation and widespread adoption of intra-arterial therapies for the treatment of acute ischemic stroke. Five clinical trials spanning multiple continents were published in early 2015 that proved that intra-arterial treatment – both with and without tPA – is beneficial in improving functional recovery after stroke. Emerging literature (including the DAWN trial) also suggests that patients can be treated up to 24 hours after the onset of symptoms based on the size of the infarct core obtained using MRI Perfusion or CT Perfusion imaging. With respect to stroke secondary prevention, widespread adoption of long-term cardiac monitoring has increased the detection rate of atrial fibrillation (as demonstrated in the EMBRACE and CRYSTAL-AF trials). Pioglitazone (an oral hypoglycemic agent of the thiazolidinedione drug class) was shown in the IRIS trial to reduce the risk of recurrent stroke in patients with impaired glucose tolerance who had not developed type 2 diabetes mellitus.

KEYWORDS: Ischemic stroke, transient ischemic attack, mechanical thrombectomy, atrial fibrillation; embolism, pioglitazone

INTRODUCTION

The last 3 years have represented a paradigm shift in the treatment and prevention of ischemic stroke. Overwhelmingly, the most important change has been a comprehensive demonstration of the efficacy of interventional treatment for acute ischemic stroke. In addition to this, there have been advances in medical therapy for the prevention of recurrent stroke, new strategies for the detection of atrial fibrillation and a plethora of new oral anticoagulants for use in the prevention of stroke of embolic origin.

INTERVENTIONAL THERAPY FOR ACUTE ISCHEMIC STROKE

The most important advance in the field of stroke neurology since the discovery of tissue plasminogen activator (tPA) occurred in 2015. Thrombus retrieval using intra-arterial therapies was demonstrated as being both safe and highly effective in the treatment of acute ischemic stroke. This has led to a rapid uptake in its use in the United States and across the world and has galvanized the neurologic community to improve systems of care and rapid access to stroke treatment centers.

The use of mechanical devices to treat acute ischemic stroke was the subject of controversy in the field of stroke neurology for over a decade. Multiple trials[1,2] had demonstrated that mechanical clot retrieval devices improved the rate at which arteries were re-canalized after an acute occlusion, but no trials had demonstrated that this necessarily improved functional outcomes. For example, the Merci device[3] (Mechanical Embolus Removal in Cerebral Ischemia) used a corkscrew mechanism to penetrate a clot and then retrieve it. (**Figure 1**) It was effective at achieving the goal of removing clots but was associated with a high rate of complications, specifically arterial dissection.

The Penumbra device[5] used a gentle suction mechanism at the proximal end of a clot to attempt to gradually retract it. (**Figure 2**) It was associated with a lower rate of complications but also never shown to improve functional outcome.

In early 2015, five clinical trials were published in quick succession demonstrating the efficacy of a new generation of devices to treat acute ischemic stroke: MR CLEAN[6], ESCAPE[7], EXTEND-IA[8], SWIFT PRIME[9] and REVASCAT[10]. These trials mostly used a stent retriever device. (**Figure 3**) This device introduces an undeployed stent directly in to the core of a clot, then expands the stent, leaving it in situ for approximately 5 minutes. This causes a clot to become enmeshed in and adherent to the stent before being extracted.

The results of the trials are depicted in **Table 1**:

A meta-analysis[11] of these trials confirmed that mechanical thrombectomy led to reduced disability at 90 days with an odds ratio of 2.49. The number needed to treat (NNT) was only 2.6 to achieve one favorable outcome. In addition, the risk of death at 90 days and the risk of cerebral hemorrhage were no higher than that of tPA alone. In the last few months, the investigators for the MR CLEAN trial showed that the benefits seen at 90 days persisted after 2 years of follow-up of their original trial subjects.[12]

Intravenous tPA and intra-arterial clot retrieval can only be delivered if a person presents within the "therapeutic

Figure 1. The Merci device[4]

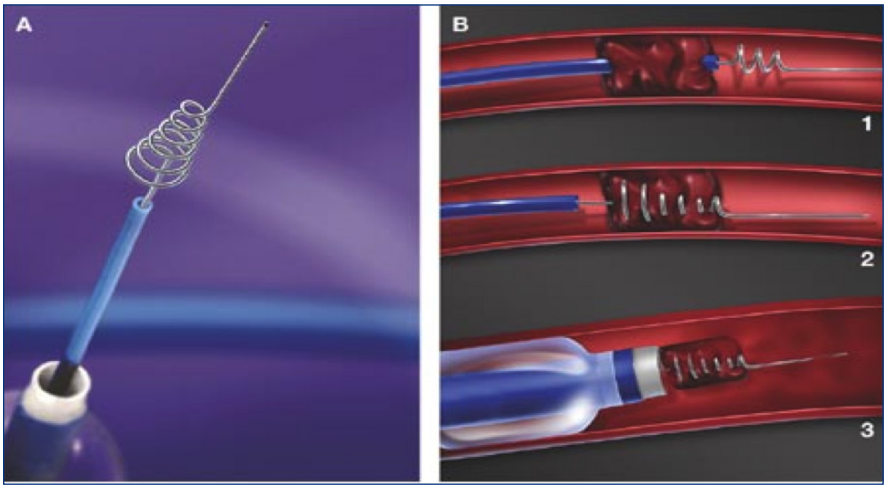


Figure 2. The Penumbra device[5].

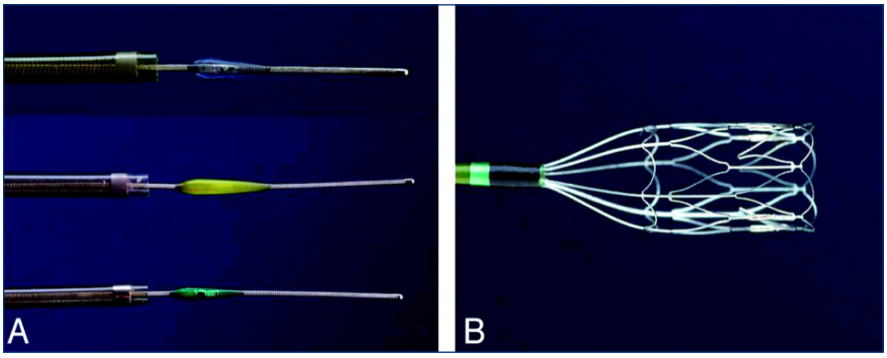
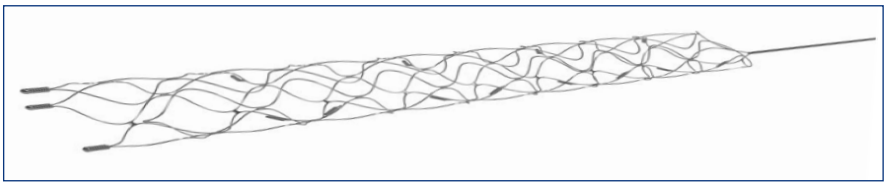


Figure 3. The Stent Retriever Device.



www.medtronic.com/us-en/healthcare-professionals/products/neurological/revascularization-stroke/solitaire.html

window" – 4.5 hours for tPA and 6–12 hours for intra-arterial therapy. Therefore, an enormous challenge in the field of stroke neurology is the treatment of strokes that present late (after 12 hours) or from sleep (so-called "wake-up strokes"). The DAWN trial[13] (Clinical Mismatch in the Triage of Wake Up and Late Presenting Stroke Undergoing Neurointervention with Trevo) was recently completed. This was a randomized, controlled trial of thrombectomy vs. best medical therapy in patients who had a stroke beginning between 6 and 24 hours prior to presentation and who would not have not strictly been eligible for treatment with intra-arterial therapy. However, in this trial the investigators performed an assessment of the size of the "core infarct" (the area of dead tissue that is felt not to be salvageable) using magnetic resonance imaging (MRI) or computed tomography perfusion (CTP) imaging. They enrolled patients with a core infarct volume of <50 cc and a large stroke syndrome (NIHSS >20) meaning that the person's stroke syndrome was worse than their imaging demonstrated, suggesting that there was a large volume of brain tissue that was salvageable. Using this protocol, they enrolled people presenting late in their "stroke window" and perform intra-arterial clot retrieval safely. Of 206 subjects, those treated with intra-arterial clot retrieval, achieved a favorable functional outcome in 48.6%, in comparison to 13.1% of patients in the control arm.

Table 1. The results of the trials.

Trial	Number of patients	Intervention	Outcome measure	Enrollment criteria	Result
MR-CLEAN(6)	500 (233 in intra-arterial treatment group vs. 267 in control group)	Stentriever	mRS at 90 days	Within 6 hours of symptom onset	OR of 1.67 for functional independent
ESCAPE(7)	316 (165 in intra-arterial group vs. 150 in control group)	Any thrombectomy device	mRS at 90 days	Within 12 hours of symptom onset	OR of 2.6 for functional independence
EXTEND-IA(8)	70 (35 patients in each group)	Stentriever	mRS at 90 days	Ischemic core of <70ml on CT Perfusion	71% functional independence in treatment group vs. 40% in control group
SWIFT PRIME(9)	196 (98 patients in each group)	Stentriever	mRS at 90 days	Within 6 hours of symptom onset	60% functional independence in treatment group vs. 35% in control group
REVASCAT(10)	206 (103 patients in each group)	Stentriever	mRS at 90 days	Within 8 hours of symptom onset	OR of 2.1 for functional independence

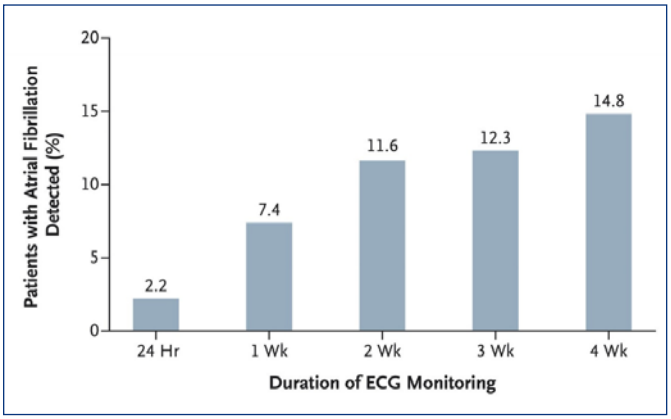
DETECTION OF ATRIAL FIBRILLATION AFTER ISCHEMIC STROKE

Approximately one-third of all strokes are labelled as cryptogenic i.e., there is no cause identified despite a comprehensive workup. There is, however, growing recognition that paroxysmal atrial fibrillation is challenging to diagnose and can easily be missed with only short-term cardiac telemetry. So, a large proportion of patients with "cryptogenic stroke" may have atrial fibrillation that has simply not been diagnosed. Since strokes due to atrial fibrillation are eminently preventable – anticoagulation with inexpensive, widely available medications such as coumadin reduce the risk of stroke due to atrial fibrillation by approximately two-thirds[14] it is important to evaluate. Even brief bouts of atrial fibrillation substantially increase the risk of stroke.[15] The fact that strokes due to atrial fibrillation are so severe – and so treatable – lends an urgency to its detection.

Two recent trials are informative in this regard:

1) EMBRACE[16]: The EMBRACE trial was a study of patients aged 55 years and above who had suffered a cryptogenic stroke or cryptogenic TIA in the 6 months preceding screening and who had no evidence of atrial fibrillation after 24 hours of cardiac telemetry. The investigators randomized them to either a further 24 hours of telemetry or 30-days of continuous ambulatory cardiac rhythm monitoring. The primary outcome measure was the detection of 30 seconds of continuous atrial fibrillation. In the intervention group, 16.1% of patients were found to have new paroxysmal atrial fibrillation in contrast to a 3.2% of patients in the control group. They also demonstrated a very clear, incremental yield with an increased length of monitoring time. (**Figure 4**)

Figure 4. Incremental yield of prolonged ECG monitoring for the detection of atrial fibrillation in patients with cryptogenic stroke or TIA.[16]



This increased rate of diagnosis of atrial fibrillation resulted in an increased rate of anticoagulant therapy: 18.6% of the intervention group vs. 11.1% of the control group. This trial highlights the fact there is a significant proportion of people who have been historically diagnosed with "cryptogenic" stroke who have probably had occult atrial fibrillation.

2) CRYSTAL-AF[17]: The CRYSTAL-AF trial examined the use of an insertable cardiac monitor (ICM) for the purpose of detecting paroxysmal atrial fibrillation. An ICM is a small device that is placed under the skin of the chest through a very minor outpatient procedure with no need for sutures or anesthesia. It has the ability to continuously monitor heart rate and remotely transmit data. The device is left in place for up to 3 years at a time and is well tolerated. The CRYSTAL-AF investigators enrolled patients aged 40 or older who had a stroke or TIA within the preceding 90 days and labelled as cryptogenic after a work-up which included 24 hours of EKG monitoring. 441 were successfully randomized to either the intervention group (ICM insertion) or the control group (with no specific protocol for heart rhythm monitoring specified). They also used the primary outcome of 30 seconds of continuous atrial fibrillation. In the patients assigned to the control group, the rate of atrial fibrillation diagnosis was only 1.4% at 6 months of follow-up whereas in the intervention group it was 8.9%. Only 2.4% of ICMs had to be removed in this study – the most common reason being local infection, pain or irritation.

The lower detection rate of atrial fibrillation in the CRYSTAL-AF study compared with the EMBRACE study may reflect the younger population that was studied in that trial. Alternatively, it could represent technical differences between the ability of and ICM and an ambulatory Holter monitor to detect atrial fibrillation. Both of these trials used 30 seconds of atrial fibrillation as a cutoff and so they may still underestimate the true prevalence of atrial fibrillation.

The growing recognition of embolism as a major cause of stroke – especially in those people diagnosed with a cryptogenic stroke – has led to the creation of a new clinical construct: embolic stroke of undetermined source (ESUS).[18] This refers to a stroke that appears embolic (i.e. it is multifocal, based in the watershed zone or cortically-based) and is too large to simply represent a lacunar infarct (i.e., is greater than 1.5cm in maximal diameter) but for which no cause can be found. The potential causes include atrial fibrillation, sub-stenotic or aortic arch atherosclerosis, and cardiac shunt. Recently, atrial dysfunction or cardiopathy in the absence of atrial fibrillation has been proposed as a mechanism in patients with ESUS. This is based on the fact that serum, ECG, and echocardiographic biomarkers of atrial cardiopathy have been shown to be associated with embolic risk in the absence of atrial fibrillation.[19] In addition, recent studies showed no temporal relationship between subclinical atrial fibrillation and embolic events, arguing that atrial fibrillation is a biomarker of atrial cardiopathy which in turn is the direct cause of stroke in most patients with this arrhythmia.[19]

INSULIN RESISTANCE AND THE SECONDARY PREVENTION OF STROKE

Insulin resistance is a phenomenon observed in those with type 2 diabetes but also in approximately half of all people without diabetes who have had a stroke or TIA. There is a rich basic science literature on the interaction between insulin resistance and atherosclerosis, inflammation and thrombosis. This generated interest in whether or not treating insulin resistance itself would aid in the secondary prevention of ischemic stroke. The IRIS trial (Insulin Resistance Intervention after Stroke)[20] was designed to test whether administration of pioglitazone (a member of the thiazolidinedione drug class of oral hypoglycemic agents) would reduce the risk of recurrent stroke. In this trial, Kernan et al[20] (2016) studied patients 40 and older who had suffered an ischemic stroke or TIA in the 6 months prior to enrollment. Specifically, within that population they studied patients with evidence of insulin resistance but not frank type 2 diabetes. Patients were randomized to either pioglitazone (at a dose of 15mg which was ramped up to 45mg if well-tolerated) or placebo. Follow-up took place over 5 years and the primary outcome was the occurrence of stroke or myocardial infarction. 3876 patients were randomized to either pioglitazone or placebo – 1939 in the pioglitazone group and 1937 in the placebo group. This trial had a positive outcome: 11.8% of patients administered placebo reached the primary outcome over the 5 year follow-up period whereas only 9.0% of the patients administered pioglitazone did. The p-value for this result was significant at 0.007. Among secondary analyses, it was also noteworthy that the rate of progression to type 2 diabetes was lower in the pioglitazone group.

The results of this trial are impressive but there are a number of important caveats:

The risk of bone fractures was high in the group treated with pioglitazone: 5.1% of patient suffered a bone fracture in the treatment group compared with only 3.2% in the control group ($p<0.003$).

All patients with stroke or TIA were included in the trial irrespective of the cause of their stroke/TIA. Stroke is the endpoint of multiple, diverse disease states and not a disease itself per se. For instance, approximately 7% of patients in this trial had atrial fibrillation. A stroke due to atrial fibrillation would not be expected to be prevented by a medication that addressed insulin resistance. This point serves to caution against prescribing pioglitazone to a patient who has suffered a stroke, prior to first carefully evaluating the mechanism of the stroke.

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Parkinson's disease: A Quick Update

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ABSTRACT

Parkinson's disease is a neurodegenerative disorder characterized by motor and non-motor symptoms. Although the diagnosis still relies on the presence of motor signs, new diagnostic criteria have been proposed to incorporate recent observations in order to improve accuracy. The cornerstone of therapy remains dopamine replacement with L-Dopa. However, new therapies, with different modes of action, or administration have become available to improve management.

KEYWORDS: Parkinson's disease, movement disorder, extrapyramidal, tremor, deep brain stimulation

BACKGROUND

Parkinson's disease (PD) is a neurodegenerative disease, characterized by motor and non-motor symptoms. The prevalence of the disease ranges from 100 to 200 per 100,000 people and its annual incidence is approximately 15 per 100,000. Men are more frequently affected than women and age of onset is variable, usually after age 50. Onset earlier than 40 years is observed in less than 5% of the cases. Aging increases the risk of developing the disease. Monogenetic forms are responsible for less than 10% of the cases, and the majority of cases are considered idiopathic. (1) In this paper, we will discuss the most recent published diagnostic criteria for PD as well as the most recent clinically available treatments.

CLINICAL DESCRIPTION

The diagnosis of PD relies mostly on clinical expertise. Recently the International Movement Disorders Society published a proposed new set of criteria (2). In summary, the first step is to diagnose the presence of Parkinsonism defined by bradykinesia (slowness of movement, and decrement in amplitude or speed on continuous movement), in combination with either rest tremor, rigidity (velocity-independent resistance to passive movement), or both.

The second step in diagnosing "clinically established PD" requires the absence of absolute exclusion criteria; the presence of at least two supportive criteria; and no "red flags." The diagnosis of clinically probable PD can be made in the absence of absolute exclusion criteria and the presence of red flags counter balanced by supportive criteria. Exclusion criteria include findings on the neurological examination suggestive of signs not seen in PD such as cerebellar, pyramidal or eye movement abnormalities. The most important red flags are rapid progression of gait and balance impairment, lack of progression of disease not attributable to treatment, and absence of any of the common non-motor features of the disease.

IMAGING STUDIES

Imaging is not helpful in diagnosing PD and is used only for atypical cases. 123I-ioflupane SPECT (DatSCAN) is approved for distinguishing essential tremor from PD and is probably also helpful, although not approved, for distinguishing drug-induced parkinsonism from PD. DaT is normal in ET and DIP. However, DaTSCAN is also abnormal in patients with other forms of primary Parkinsonism which attack the dopaminergic cells in the basal ganglia (3) Therefore DaT, if normal, excludes the diagnosis of PD but a positive scan does not make the diagnosis.

TREATMENT

PD treatment involves a combination of life style measures, medication and, in some cases, surgery. In the following section, we will discuss newer therapeutic interventions.

Exercise

Exercise improves motor and non-motor symptoms, such as pain, sleep and mood. Most experts agree that exercise should be encouraged as part of the treatment (4). There are no data to suggest an optimal exercise strategy, so that common sense dictates that the regimen chosen should: (a) take into consideration safety, motor and cognitive constraints and other medical comorbidities; (b) be an activity the patient is comfortable with; (c) be one the patient will likely adhere to.

Medication

The choice of the initial therapy of patients with PD takes into account age, employment status, presence of comorbidities, cognitive status, active psychiatric issues, and patient

preference. There are no therapies known to slow disease progression. Even though there is no consensus on the best time for therapy to be initiated, there is also no reason to withhold therapy in those with clear symptoms in order to prevent future treatment-related complications.

Motor symptoms

1) Levodopa: A precursor in dopamine synthesis remains the superior drug in symptom control. A new formulation of carbidopa/levodopa is available. Rytary (Impax Laboratories, Hayward, CA, USA) is an oral, extended-release capsule that contains beads of levodopa and carbidopa with differing rates of absorption, allowing for a decreased dosing frequency. Rytary is FDA approved for both drug naive patients and those with motor complications by increasing "on" times, without worsening troublesome dyskinesias. Its side effect profile and tolerability are similar to other levodopa preparations. (5, 6) There are no long-term data on starting patients directly on Rytary compared to immediate release (IR) levodopa. The major indication to switch a patient from the IR formulation to Rytary is the presence of wearing off, especially if the patient is already receiving IR at a frequency of over 4 doses a day. The ratio for conversion is approximately 2:1 (Rytary: IR levodopa), and it can be done overnight. Since part of the formulation contains IR granules, patients should be advised to avoid taking medication with food (at least 30- minute interval). Rytary can take up to 8 weeks for the full benefit to be observed after the switch, and dose adjustments are usually required (7).

2) Dopaminergic agonists (DA): DA bind to post-synaptic dopamine receptors. They can be used as monotherapy in patients with early disease or as adjunctive therapy in later disease stages. The main adverse effects are nausea, vomiting, edema, hypotension, excessive daytime sleepiness and sleep attacks, impulse control disorders and hallucinations, especially in elderly patients. The most commonly used are pramipexol, ropinirole and rotigotine. Apomorphine has a different profile from other agonists with potent D1 and D2 agonist action. Apomorphine is available as an intermittent injection and in other countries as a continuous infusion. It has poor bioavailability after oral ingestion. The ideal subjects are on an optimized oral schedule, are able to both recognize their "off" state and to inject themselves (or have a caregiver to do it). Indications are the need for rescue medication (early morning "off", delayed "on", unpredictable "offs") or gastroparesis. Subcutaneous apomorphine is rapidly absorbed and peak plasma concentration is achieved in 10 to 20 minutes, with a clinical effect lasting from 45 to 60 minutes. First apomorphine injection should be monitored particularly for hypotension and nausea. Side effects include nausea, injection site reactions, postural hypotension, confusion, psychosis, impulse control disorders, and rarely hemolytic anemia and eosinophilic syndrome. (8) Nausea is so common that an antiemetic is always started before the first dose, and is required for ongoing treatment in about half the cases.

3) MAO-B inhibitors increase dopamine availability by inhibition of monoamine oxidase B, which metabolizes dopamine. They can be used as monotherapy in mildly symptomatic young subjects or as adjunctive therapy. Side effects include nausea, vomiting and insomnia (selegiline). Safinamide (XADAGO), the newest agent, has dopaminergic action, by selective and reversible inhibition of MAO-B, and nondopaminergic properties due to voltage-gated sodium and N-type calcium channels inhibition, modulating glutamate release. It is indicated as adjunctive treatment in patients with PD experiencing "off" episodes, as it increases "on-time" with no increase in bothersome dyskinesias. Efficacy as monotherapy has not been established. Common adverse events (AEs) include dyskinesia, insomnia, somnolence, dizziness, headache, cataract, orthostatic hypotension, nausea and falls. (9, 10) Relative efficacy of MAO-b inhibitors is unknown. Safinamide is a reversible MAO-b inhibitor, unlike selegiline and rasagaline. Thus the effects of safinamide begin much sooner than the older drugs, and resolve much sooner if discontinued.

4) Amantadine: amantadine extended release capsules (GOCOVRI) is the first and only FDA-approved medicine for treatment of dyskinesia in patients with Parkinson's disease receiving levodopa therapy, with or without concomitant dopaminergic agents. It reduces both off times and well as levodopa-induced dyskinesias in PD patients with dyskinesias (11). There are no data to determine if this formulation is more effective than the generic form of the drug, which is usually given 2 or 3 times daily.

Non-motor symptoms

1) Pimavanserin: is a selective 5-HT_{2A} inverse agonist with a lower affinity for 5-HT_{2C} and sigma-1 receptors. It lacks dopaminergic, muscarinic, adrenergic, and histaminergic activity. (12) Data suggests a high benefit/risk profile with number need to treat (NNT) <10 (using a very conservative definition of improvement), number needed to harm (NNH) was ≥ 10 (although not statistically different from placebo) and the likelihood to be helped by taking the medication was consistently over 1 (13). Pimavanserin is the only drug with FDA approval for the treatment of hallucinations and delusions associated with PD psychosis. (12)

2) Droxidopa: is an oral norepinephrine precursor approved for the treatment of neurogenic orthostatic hypotension caused by primary autonomic failure. Studies show a good safety profile with NNT <10, NNH from 23-302. Droxidopa is 7.8 times more likely than placebo to provide clinical benefit than drug discontinuation due to an adverse event. (14) Droxidopa has been studied in patients with PD showing similar results, leading to decreased number of falls and increased standing systolic blood pressure. (15, 16)

Device-aided treatments

Response to levodopa is a prerequisite for all therapies below as neither is helpful in patients not responsive to the drug. Patients with drug-resistant tremor may respond well to DBS, though, when L-Dopa is not helpful.

1) Levodopa–carbidopa intestinal gel (LCIG) is an aqueous gel containing a combination of levodopa and carbidopa (20 mg and 5 mg respectively per milliliter) delivered directly to the proximal jejunum *via* a percutaneous endoscopic gastrostomy tube with a jejunal extension connected to a portable, programmable infusion pump. By bypassing gastric emptying, levodopa is steadily absorbed producing stable plasma concentrations, thus decreasing motor complications (dyskinesia and motor fluctuations). Dose is individually titrated, and after a morning bolus a continuous infusion is administered over 16 hours, with further bolus if necessary. LCIG may be administered as monotherapy, or with adjunctive therapies. The treatment may be continued for as long as it is beneficial. Procedure/device related adverse events are reported in 76% of subjects; 17% of those are considered serious. Most frequent non-procedure/device adverse events are dyskinesias, chronic polyneuropathy (due to vitamin B deficiencies), stoma infection and weight loss. (17, 18)

2) DBS: The two main sites of DBS placement are the subthalamic nucles (STN) and the globus pallidus (GPi). STN-DBS improves off-drug score compared with preoperative off-drug condition; decreases off-time during the day; improves quality of life; and allows the decrease in levodopa equivalent daily dose resulting in the reduction in levodopa-induced dyskinesia. (19) A recent analysis in the German health care system suggested that STN-DBS at earlier stages of the disease is cost effective in patients younger than 61 years when compared with the best medical treatment (20). GPi-DBS also provides improvement in motor scores associated with reductions in dyskinesias with modest or no decrease in dopaminergic therapy. Complications of DBS are either related to surgery, implanted material or by stimulation itself. Severe adverse events such as death or permanent disability are rare, and occur in less than 2% of the cases, while hardware-related adverse events are observed in 9% of the cases. Much more common are reversible adverse effects of stimulation, which may happen in up to 20% of patients. Long-term follow-up demonstrates sustained benefits of STN-DBS and GPi-DBS despite disease progression. Practitioners should be aware that DBS does not slow disease progression and should be considered another symptomatic therapy. It is considered a stand-of-care treatment, covered by all insurers.

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Fighting Fire with Fire: Surgical Options for Patients with Drug-Resistant Epilepsy

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ABSTRACT

While antiepileptic drugs (AEDs) provide adequate seizure control for most patients with epilepsy, ~30% continue to have seizures despite treatment with two or more AEDs.[1] In addition to direct harm from seizures, poor epilepsy control correlates with higher mortality, morbidity, [2,3] and cost to the healthcare system.[4] In the subset of patients with persistent seizures despite medical management, surgical intervention and neuromodulation may be more effective. Primary care physicians and general neurologists should be aware of non-AED treatment options that are standard of care for drug-resistant epilepsy (DRE).

KEYWORDS: Drug-resistant epilepsy, surgical treatment of epilepsy, vagal nerve stimulation, responsive neuro-stimulation

DRUG-RESISTANT EPILEPSY: ITS CONSEQUENCES

Epilepsy affects ~1% of the United States population.[1] Despite an expanding selection of AEDs, many patients continue to have seizures, even with AED polypharmacy.[1] The International League Against Epilepsy (ILAE) defined drug-resistant epilepsy (DRE) as failure of adequate trials of two appropriate, well-tolerated antiepileptic medications (whether as monotherapies or in combination) to achieve sustained seizure freedom.[5]

DRE is associated with higher long-term morbidity and mortality[3] including sudden unexplained death in epilepsy (SUDEP), accidental injury and death, cognitive decline, as well as psychiatric and psychosocial comorbidities.[2] SUDEP is defined as non-traumatic, non-drowning-related sudden death in a person with epilepsy which may or may not be related to recent seizure but is not due to status epilepticus, with autopsy that is unrevealing of an obvious anatomic or toxic cause of death,[6] and is thought to be related to seizure-induced cardiac arrhythmias. SUDEP is the most common epilepsy-related cause of death, with an incidence of up to 9.3 deaths per 1000 person-years among some with DRE.[6] The strongest risk factor for SUDEP is recurrent seizures.[6]

Seizures impede patients' freedom to pursue education and careers,[7] drive,[6] and live independently. AED side effects can also adversely affect quality of life (QOL),[8] and have implications for patients' overall health. Patients with DRE require more ER visits and hospitalizations, longer hospital stays, more office visits, and accumulate up to double the healthcare costs of those with stable epilepsy.[4]

EPILEPSY CENTERS

Neurologists differentiate seizures that are "generalized" in onset (e.g. seizures arising from the entire brain at onset) from those that are "focal" or "partial" (e.g. seizures starting from one part of the brain). Classification systems for epilepsy are complex, relying on factors including clinical history, physical examination, EEG and MRI findings. Therefore, all patients with epilepsy should have a neurologist, preferably one with additional training in epilepsy. The National Association of Epilepsy Centers (NAEC) recognizes four levels of epilepsy care. Level 1 care consists of evaluation at an emergency department or primary care office, while level 2 care involves assessment by a general neurologist. Levels 3 and 4 are offered at specialized epilepsy centers, which provide a comprehensive approach to DRE.[9] The NAEC recommends referral to an epilepsy center if seizure freedom is not achieved within one year of treatment.[9] Earlier referral is recommended if the epilepsy diagnosis is in question, or in the following additional situations: to distinguish epileptic from psychogenic non-epileptic events; to optimize seizure control in non-refractory patients; to integrate neurologic and psychiatric care; and to optimize AED management for family planning. Other epilepsy center services include surgical evaluation, counseling on epilepsy-related dietary modifications, and care for developmental disabilities. The Brown-Rhode Island Hospital Comprehensive Epilepsy Program is a level 4 epilepsy center.

PREOPERATIVE EVALUATION

DRE rates are higher in focal epilepsy (35%) than in generalized epilepsy (25%).[6] Some focal epilepsies are associated with an underlying lesion, such as a stroke, tumor or vascular malformation, whereas others lack an overt structural abnormality apparent on MRI. Feasibility of surgical intervention should be explored as soon as focal DRE is diagnosed, since intervention can result in seizure reduction or seizure-freedom, with associated potential benefits including improved morbidity and mortality, better QOL, improved

psychiatric outcomes, and decreased AED requirement.[1,3]

Preoperative workup includes long-term video EEG monitoring and high-resolution brain MRI. Further investigations can include positron emission tomography, single photon emission computed tomography (SPECT), magnetic resonance spectroscopy, subtraction ictal SPECT co-registered to MRI, functional MRI, and magnetoencephalography.[10] In many cases, patients initially diagnosed with 'non-lesional' epilepsy are found to harbor a subtle lesion using these techniques.

Neuropsychological testing is used to assess for potential preoperative cognitive impairments and to predict postoperative neuropsychological outcomes.[10] For patients with temporal lobe epilepsy (TLE), Wada testing defines language localization and risk-stratifies the patient regarding possible postoperative memory impairment.[10] This test involves anesthetizing one hemisphere while a neuropsychologist performs rapid testing to characterize language and memory function in the contralateral hemisphere.

Our epilepsy center conducts multidisciplinary conferences to review potential surgical candidates. This forum draws upon the expertise of specialists from epilepsy, neurosurgery, neuroradiology and neuropsychology departments to formulate an individualized approach for each patient. Depending on the patient's needs, the team may include other specialists such as a psychiatrist, nutritionist, and social worker.

After the first phase of preoperative testing, some patients are found to be good surgical candidates and are referred to neurosurgery. Other patients may be deemed poor candidates for resective or ablative surgery for various reasons, such as the determination that the seizure focus stems from an important structure needed for language or mobility, or the finding of seizures from multiple foci. However, recent advances in the treatment of epilepsy offer hope for patients facing these difficult situations. Alternatives include an ever-growing list of AEDs, hormonal treatments, low glycemic index dietary approaches, and neuro-stimulation devices.

SURGICAL OPTIONS AND OUTCOMES IN EPILEPSY

Temporal lobe epilepsy (TLE) is among the most common focal epilepsies,[11] and is sometimes associated with scarring of the mesial structures including the hippocampus, called mesial temporal sclerosis (MTS). TLE is the focal epilepsy syndrome most amenable to surgery, and anterior temporal lobectomy (ATL) is the most common epilepsy surgery.[12] Therefore, many studies of surgical outcomes in focal epilepsy have emphasized the study of TLE patients who undergo ATL. Classically, ATL consists of the removal of some anterior-lateral temporal cortex plus resection of the amygdala, para-hippocampal cortex, and hippocampus.[9,12] Many such patients have MTS demonstrated on MRI and this subgroup has historically done extremely well with surgical intervention. More recently, selective ablation of the mesial temporal lobe structures (hippocampus and amygdala) using laser-thermal technology has demonstrated nearly equivalent outcomes for seizure control and improved neuropsychological outcomes due to sparing of lateral neocortical structures and adjacent white matter tracts.[13, 14] Other surgeries for focal epilepsy include topectomy, in which cortex is removed while sparing underlying white matter, as well as lesionectomy, extratemporal lobar or multilobar resections, multiple subpial transection, and hemispherectomy.

In a landmark randomized controlled trial (RCT) of surgical versus medical management in patients with drug-resistant TLE, resection resulted in seizure-freedom in 58% when evaluated one year after surgery, compared with 8% with medical management;[7] a second RCT demonstrated 73% seizure-freedom after two years of follow-up among patients who had surgery within two years of developing DRE, compared with 0% seizure-freedom in medically-managed patients.[1] Approximately 45% of patients were seizure-free after resection for extra-temporal lobe epilepsy.[1]

Data suggest that the earlier the surgery, the better the outcome.[1] Sex and age do not affect surgical outcomes.[1] While older age was previously thought to be a relative contraindication to epilepsy surgery, a retrospective analysis of ATL for MTS showed that age at surgery did not independently affect seizure recurrence.[8] Although patients with an identifiable lesion are more likely to experience postoperative seizure reduction or seizure freedom,[1] patients with non-lesional DRE can also benefit from surgery if seizures are well-localized on EEG.

Even when patients do not achieve total seizure-freedom postoperatively, reduction in seizures can be quite significant. A meta-analysis of studies of medically refractory TLE cases treated with surgical resection at 13 centers, 67.2% of patients achieved seizure-freedom and an additional 20% experienced improvement.[7] Thus, 87% of the patients achieved significant seizure reduction with surgery. Many patients with DRE experience numerous seizures each day, so reduction in seizure burden can be life-changing for patients and caretakers. Additionally, a systematic review of QOL for adults after epilepsy surgery has shown that QOL is significantly improved after surgery, with the most significant gains seen in those attaining seizure-freedom.[1]

NAEC-published data indicates that of the ~750,000 patients in the USA with DRE, a mere 2,459 patients, on average, underwent resection surgery each year from 2012 through 2015.[15] Several factors limit the identification and treatment of potential surgical candidates. First, many with DRE are not referred to an epilepsy center. DRE patients also vary in the degree to which seizures are disabling, and may forgo evaluation if the patient and treatment team feel that the seizures are not disruptive or limiting to quality of life.

SURGICAL RISKS AND ALTERNATIVES

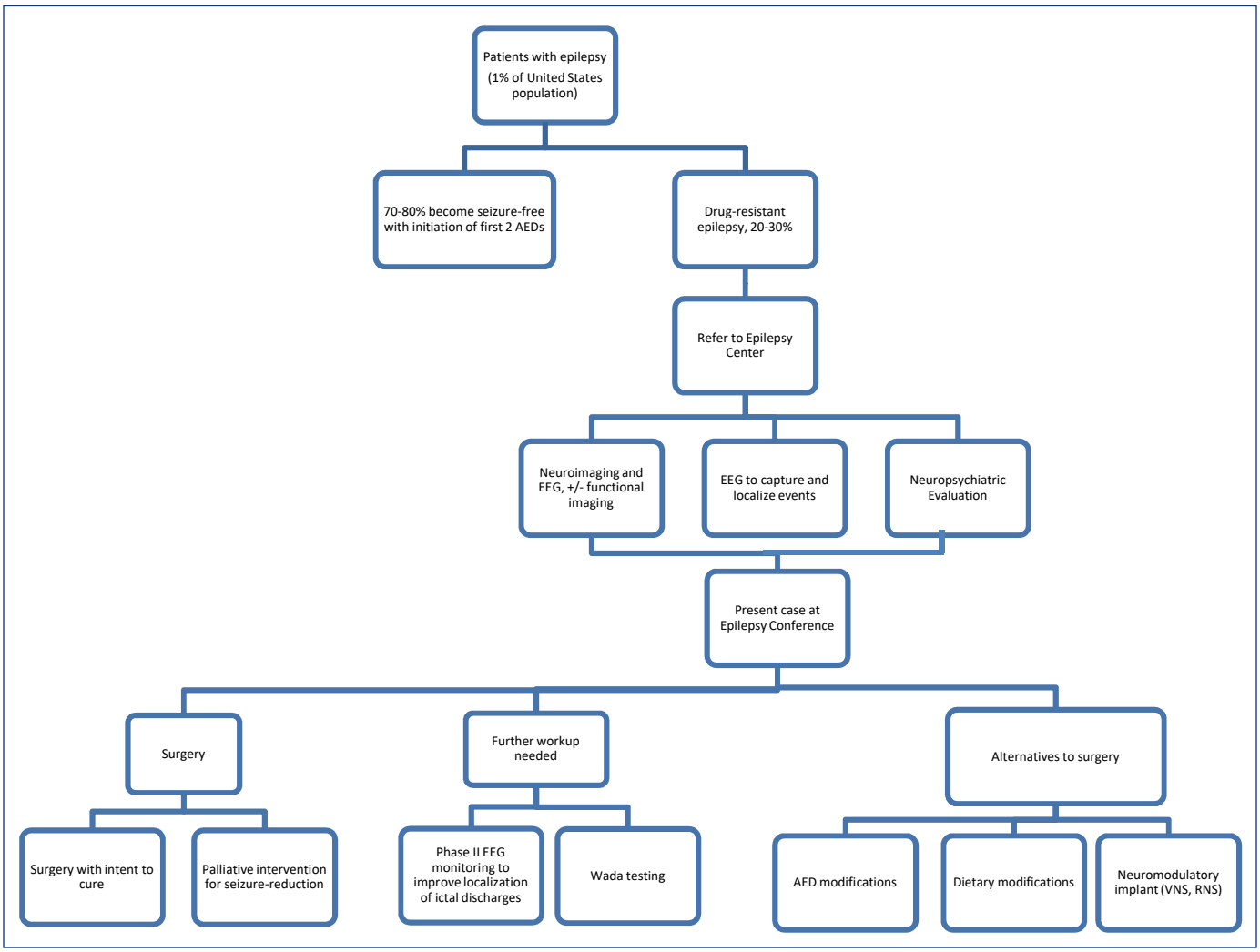
Risks associated with epilepsy surgery are defined by the location of the epileptic focus. For example, TLE surgery is

associated with risks of language deficit, memory impairment, motor impairment, visual field cut, cranial nerve injury, and behavioral/personality changes depending on the location of the focus.[10] With newer, less invasive and more tissue-sparing techniques for epilepsy surgery, the incidence of these has decreased. Reviews of epilepsy surgery have shown that operative mortality ranges from 0.1% to 0.5%.[1]

Apart from resective surgery, alternative options include vagus nerve stimulation (VNS) or responsive neuro-stimulation (RNS). VNS is an option to treat DRE which is not amenable to conventional resection, and for patients with persistent DRE after surgical resection.[12] VNS implantation involves surgical placement of a generator below the clavicle, with a stimulating wire connected to the left vagus nerve, to deliver intermittent stimulation.[12] The mechanism of action of VNS is speculated to relate to desynchronization of cortical activity.[16] A meta-review of 14 VNS outcomes studies demonstrated that ~50.9% of patients achieved a >50% reduction in seizure frequency.[16] The efficacy of VNS increases over approximately two years following implantation.[17] Bilateral or multifocal epilepsy may be associated with even better VNS outcomes.[18] Common but generally tolerated side effects include hoarseness and neck-tingling.[16]

RNS was FDA-approved in 2013 for patients 18 years or older with focal DRE and no more than two epileptic foci. RNS implantation involves neurosurgical placement of subdural or depth electrodes near the focus. Seizure pattern-detectors in the device are programmed to trigger direct cortical stimulation upon detection of an ictal buildup.[19] Electrical stimulation at the onset of ictal discharge is intended to interrupt propagation of the discharge before the seizure generalizes and the patient becomes symptomatic. The RNS System Pivotal trial, a multicenter RCT to evaluate short-term efficacy of RNS versus sham treatment, demonstrated a 37.9% decrease in mean seizure frequency in the treatment group, compared to 17.3% seizure reduction in the control group.[17] Patients receiving RNS treatment demonstrated statistically significant improvements in verbal functioning, visuospatial ability, memory, social function, health concerns, and

Figure 1. General approach to evaluation in DRE



cognition at one and two years post-implantation.[19] There were also significant improvements in QOL scores.[19] Some common complications and side effects of RNS noted during the Pivotal trial included implant site pain, local swelling or infection, headache, and dysesthesia.[19] Another disadvantage is the necessity of repeated surgery for battery changes, with an average battery life of 3.8 years.

CONCLUSIONS

The care of patients with DRE necessitates a multidisciplinary approach with integrated access to specialized diagnostic tools that guide the care team toward individualized treatment plans for each patient. Surgery is helpful for a subset of DRE patients. Many patients can achieve seizure-freedom after surgery. In those not achieving complete seizure-freedom, surgery can lead to a meaningful reduction in seizures, reduce risk of seizure-associated injury, and allow for reduction in medication burden. Even when the patient is disinterested in or hesitant to pursue surgery, referral to an epilepsy center can help to optimize the AED regimen, manage comorbidities and AED complications, manage key life transitions that affect epilepsy care, and explore neuromodulation among other options.

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