

# UPDATE IN MOVEMENT DISORDERS

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Movement disorders are a heterogeneous group of conditions that may be divided into hypokinetic (for example, Parkinson's disease, progressive supranuclear palsy) and hyperkinetic (for example, dystonia, Huntington's disease) conditions. Etiologies are diverse, including neurodegenerative disorders, structural (vascular, mass) lesions, autoimmune conditions, toxins, and others. In this presentation, we will examine important advances over the past 1-2 years in the most common movement disorder conditions: Parkinson's disease, essential tremor, and dystonia.

## **Update in Parkinson's disease**

Parkinson's disease (PD) is an age-related neurodegenerative disease in which there is loss of dopamine input to the striatum from the substantia nigra pars compacta. Cardinal motor symptoms are bradykinesia, rigidity, tremor in most, and later postural instability. Despite multiple medications approved for symptomatic therapy, end-of-dose wearing off of levodopa remains difficult to treat in moderate-to-advanced PD, and a variety of non-motor symptoms remain an important source of disability.

### Newly approved medications and selected clinical trials:

Pimavanserin (FDA-approved April 29 2016): a 5HT<sub>2A</sub> receptor inverse agonist that improves symptoms of Parkinson's disease psychosis [1]

Levodopa formulations: Carbidopa/levodopa extended release capsules (Rytary) and levodopa/carbidopa intestinal gel (LCIG) infusions (Duopa) are recently approved (2015). LCIG is now in testing for effects upon dyskinesia (NCT02799381). Novel formulations are currently in development [2].

- XP21279—novel LD prodrug that is absorbed in the small and large intestine by high-capacity nutritional transporters
- Accordion Pill—multilayer biodegradable films within a capsule that dissolves in the stomach, allowing the layers to unravel slowly in the stomach
- DM-1992—bilayer tab of IR/ER with gastroretentive system
- LD/CD Microtablets (Sensidose)—frequent dispensing of microtablets with sensor with built in diary and memory system allowing individualized drug delivery
- Subcutaneous LD (Neuroderm)—continuous delivery with small patch-based systems
- Inhaled Levodopa—oral inhaler in which capsule is placed resulting in puncture and release of contents—fast absorption resulting in rescue potential
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Apomorphine infusion: although well established as a treatment in other countries (and the “EARLY-PUMP” study is slated to begin in Europe) apomorphine is currently only approved as a rescue therapy by injection in the USA. A US clinical trial of apomorphine infusion is currently recruiting (NCT02339064).

Safinamide phase 3 clinical trial: this drug has reversible MAO-B inhibitor activity, in addition to anti-glutamate properties [3].

Opicapone clinical trial: opicapone is a catechol-O-methyl transferase inhibitor, as are tolcapone and entacapone, but is administered once daily and provides almost one hour decrease in “off” time daily as an adjunct to levodopa [4].

Anti-synuclein immunotherapy: several antibodies are effective in mouse models and early phase clinical trials are now underway, including PD01A [5]

Nilotinib: this drug is approved for chronic myeloid leukemia, and has BCR-abl tyrosine kinase inhibitor activity, shown to degrade misfolded alpha-synuclein by autophagy. An open label clinical trial in 12 patients with PD or DLB garnered extensive press coverage for improved motor function seen at 6 months [6].

### Surgical advances

Deep brain stimulation is now the standard-of-care for eligible patients with hard-to-manage motor complications [7]. New advances include the use of intra-operative MRI and frameless DBS, as well as changes to programming parameters and to the devices themselves:

- Low frequency stimulation [8]
- Directional lead device [9]
- Closed loop DBS

Magnetic resonance –guided Focused Ultrasound (MRgFUS) provides a novel approach to “non-incisional” lesioning (see Update in Essential Tremor), and is now in early phases of testing.

There is a resurgence of interest in neurorestorative approaches, with trials in Europe (TRANSEURO) and in Australia (neural precursor cells derived from parthenogenetic stem cells, approved in 2016 for clinical trial), and multiple groups in preclinical phase testing.

### **Update in essential tremor (ET)**

Despite numerous available medications to treat ET, many patients either cannot tolerate the drugs due to their side effect profile, or may have medication-refractory tremor. DBS is highly effective in many of these patients. However, Magnetic resonance –guided Focused Ultrasound (MRgFUS), a sophisticated means of lesioning (thalamotomy) without the need for incisions, gained FDA approval in 2016 for treatment of ET. Following open label studies that supported its efficacy, a pivotal sham surgery-controlled study of 76 patients with moderate-to-severe ET refractory to medical therapy was reported in 2016. MRgFUS was superior to sham surgery in hand tremor improvement at 12 months, and the procedure also improved quality of life and disability ratings. Side effects included sensory and gait disturbances (14% and 9% at 12 months). [10]

Attempts to define the genetic basis of ET continue, and in 2016 a large GWAS study of 2807 patients and 6441 controls demonstrated association of markers in the serine/threonine kinase STK32B gene and the transcriptional coactivator PPARGC1A [11]. However, they did not confirm previous findings of SNP associations with ET in the SLC1A2 and LINGO1 genes.

### **Update in dystonia**

Botulinum toxin injection remains first line therapy for many forms of dystonia, in particular focal dystonias such as cervical dystonia. EMG-guidance has been found helpful in certain circumstances, but there is now growing interest in whether ultrasound guidance could improve outcomes by providing direct, non-invasive and real-time visualization of muscles to be injected.

DBS targeting the GPi has long been used in management of generalized dystonia. However its use in focal dystonias has been less well defined. A recent metaanalysis of 24 studies that included idiopathic and inherited isolated dystonias, however, found significant improvement, particularly in those with younger age and greater severity at baseline [12]. A recent study of DBS targeting STN is also encouraging for those with isolated dystonia, with 3 year follow up demonstrating significant and sustained improvement [13].

An increasing number of genes are being identified for Mendelian forms of isolated and combined dystonias [14]. First reported in 2014 as a novel cause of craniocervical dystonia, mutations in the GNAL gene (DYT25), gene mutations have been found in both inherited (homozygous mutations in childhood onset generalized dystonia), seemingly sporadic craniocervical dystonia, and a GNAL mutation carrier with isolated laryngeal dystonia was recently reported [15]. DYT 26 is now known to be caused by autosomal dominant mutations in the KCDT17 gene [16], leading to myoclonus dystonia. Recessive mutations in COL6A3, a collagen VI gene, have been identified as a genetic cause of isolated dystonia (DYT27) in 2015, with subsequent report of a small number of cases with onset from childhood to early adulthood, and involving focal, segmental, or generalized dystonia [17]. However a recent report failed to confirm these findings and further studies are required. DYT 28 mutations (KMT2B: Lysine-Specific Histone Methyltransferase 2B) have been reported in 2016 as a cause of early-onset generalized dystonia, and a recent series of 27 unrelated patients describes associated phenotypic and imaging features [18].

## Telemedicine and remote monitoring in movement disorders

There is increasing interest in the use of telemedicine in movement disorders [19, 20]. Not only may this increase access to clinical care, but it is also likely to provide an adjunct to face-to-face evaluation for patients engaged in clinical trials [21]. For objective measures, multiple devices now exist that will objectively measure various features of movement, such as gait (reviewed by [22]), and the “mPower” study demonstrated how use of apps facilitates gathering data from patients “in the wild” by use of surveys and sensor-based recordings. [23]

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