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***Our Mission:*** Helping to prepare Iowa's health practitioners to care for our growing population of elders. *E-NEWS* is one of our methods of teaching through technology.

Each month, *E-NEWS* delivers abstracts from current multidisciplinary healthcare journal articles related to a specific geriatric topic. This month's *E-NEWS* focuses on OPTIMAL MEDICATION MANAGEMENT IN MOVEMENT DISORDERS.

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## OPTIMAL MEDICATION MANAGEMENT IN MOVEMENT DISORDERS

In this issue of the *E-NEWS*, you will find abstracts for:

- An article that discusses the treatment of essential tremor with high-dose thiamine.
  - An article that examines the use of  $\alpha 2\delta$  ligands for restless legs syndrome/Willis-Ekbom disease.
  - An article that presents guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease.
  - A study that assesses the tolerability and effectiveness of propranolol in treating tardive dyskinesia.
  - An article that provides a guide to medication management of movement disorders.
  - A study that evaluates opicapone as an adjunct to levodopa therapy in patients with Parkinson's disease.
  - An article that reviews the use of extended-release oral capsule of carbidopa-levodopa in Parkinson's disease.
  - A review that addresses the use of levodopa combinations in the long-term management of Parkinson's disease.
  - A study that seeks to determine the patterns of medication use in dystonia treatment.
  - A study that investigates the safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson's disease and motor fluctuations.
  - An article that explores the medical treatment of dystonia.
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- Costantini A. High-dose thiamine and essential tremor. *BMJ Case Rep.* 2018 Mar 30;2018. pii: bcr-2017-223945.

Essential tremor is a common neurological disease. The medical treatment of this affection currently involves the use of propranolol, primidone and other drugs. These drugs, however, are often not effective in reducing tremor and cause side effects in a large share of the patients treated. The treatment with intramuscular high-dose thiamine has led to a rapid, remarkable and persistent improvement of the symptoms in two patients with essential tremor. This result suggests the possibility that high doses of intramuscular thiamine may be an affordable alternative, highly effective and long-lasting medical treatment that has shown no relevant side effect.



- Faulkner MA. Use of  $\alpha 2\delta$  Ligands for Restless Legs Syndrome/Willis Ekbohm Disease. *CNS Drugs.* 2018 Feb;32(2):149-159.

Restless legs syndrome is a common neurological condition affecting a substantial portion of the population. It can be an idiopathic disorder, or one that is secondary to another cause. Given that the underlying pathophysiology of restless legs syndrome is not well understood, several drug classes have been studied for symptom control. While dopamine agonists have long been the mainstay of first-line treatment for restless legs syndrome, recently, the  $\alpha 2\delta$  ligands have been increasingly used. These agents have proven both efficacious and safe in a number of clinical trials. Additionally, compared with the dopamine agonists, they have been associated with less augmentation, a phenomenon whereby symptoms emerge earlier in the day, become more severe, and may spread to areas of the body previously unaffected. Newer clinical guidelines for restless legs syndrome are increasingly recommending the  $\alpha 2\delta$  ligands as a logical first-choice medication for patients needing drug therapy for symptom control.



- Garcia-Borreguero D, Silber MH, Winkelmann JW, Högl B, Bainbridge J, Buchfuhrer M, Hadjigeorgiou G, Inoue Y, Manconi M, Oertel W, Ondo W, Winkelmann J, Allen RP. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbohm disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. *Sleep Med.* 2016 May;21:1-11.

A Task Force was established by the International Restless Legs Syndrome Study Group (IRLSSG) in conjunction with the European Restless Legs Syndrome Study Group (EURLSSG) and the RLS Foundation (RLS-F) to develop evidence-based and consensus-based recommendations for the prevention and treatment of long-term pharmacologic treatment of dopaminergic-induced augmentation in restless legs syndrome/Willis-Ekbohm disease (RLS/WED). The Task Force made the following prevention and treatment recommendations: As a means to prevent augmentation, medications such as  $\alpha 2\delta$  ligands may be considered for initial RLS/WED treatment; these drugs are effective and have little risk of augmentation. Alternatively, if dopaminergic drugs are elected as initial treatment, then the daily dose should be as low as possible and not exceed that recommended for RLS/WED treatment. However, the physician should be aware that even low dose dopaminergics can cause augmentation. Patients with low iron stores should be given appropriate iron supplementation. Daily treatment by either medication should start only when symptoms have a significant impact on quality of life in terms of frequency and severity; intermittent treatment might be considered in intermediate cases. Treatment of existing augmentation should be initiated, where possible, with the elimination/correction of extrinsic exacerbating factors (iron levels, antidepressants, antihistamines, etc.). In cases of mild augmentation, dopamine agonist therapy can be continued by dividing or advancing the dose, or increasing the dose if there are breakthrough night-time symptoms. Alternatively, the patient can be switched to an  $\alpha 2\delta$  ligand or rotigotine. For severe augmentation the patient can be switched either to an  $\alpha 2\delta$  ligand or rotigotine, noting that rotigotine may also produce augmentation at higher doses with long-term use. In more severe cases of augmentation an opioid may be considered, bypassing  $\alpha 2\delta$  ligands and rotigotine.



- Hatcher-Martin JM, Armstrong KA, Scorr LM, Factor SA. Propranolol therapy for Tardive dyskinesia: A retrospective examination. *Parkinsonism Relat Disord.* 2016 Nov;32:124-126.

OBJECTIVE: To examine the tolerability and effectiveness of propranolol in treating tardive dyskinesia (TD).  
BACKGROUND: TD is a disabling, often irreversible, movement disorder that results from chronic therapy with dopamine receptor blocking drugs. There are no treatments currently approved for this disorder. Propranolol, a  $\beta$ -adrenergic blocker, has been reported to alleviate TD in case series and reports. METHODS: Retrospective database search of the Emory movement disorder clinic for TD patients treated with propranolol. All patients identified with at least one follow-up evaluation had records reviewed and responsiveness assessed. Logistic regression analysis examined for predictors of response. RESULTS: Forty-seven patients were analyzed, mean age 63 years. Neuroleptics were discontinued in all patients and duration of TD at the time propranolol was initiated 17 months. Mean severity of TD, based on a 0-3 scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) was 2.2. Mean response, based on a 0-3 scale (0 = no response, 1 = mild response, 2 = moderate response, 3 = complete or near-complete response) was 1.4. Propranolol resulted in improvement in 64% and 77% of those had a moderate to complete or near-complete response. Mean daily dose was 69 mg and duration of therapy 14 months. Three patients stopped the propranolol due to adverse effects: hypotension (2), nightmares (1). Severity of TD and duration of propranolol therapy were associated with response. CONCLUSION: Low dose propranolol appears to be well tolerated and effective in treating TD. A prospective randomized trial is warranted. © Elsevier Ltd.

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- Julius A, Longfellow K. Movement Disorders: A Brief Guide in Medication Management. *Med Clin North Am.* 2016 Jul;100(4):733-61.

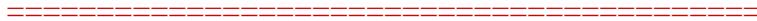
Movement disorders can be challenging to manage and often use a specific set of medications. Because it is a complex and broad field within neurology, many providers are unfamiliar with the classes of medications. This paper details medications used for specific conditions, explains why these medications are helpful, and shares pearls and pitfalls related to each agent, focusing on parameters such as dose titration, side effect profiles, and specific drug-drug interactions and challenges. We focus on the most commonly encountered movement disorders, including essential tremor, Parkinson's disease, rapid eye movement sleep behavior disorder, and restless leg syndrome.

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- Lees AJ, Ferreira J, Rascol O, Poewe W, Rocha JF, McCrory M, Soares-da-Silva P; BIPARK-2 Study Investigators. Opicapone as Adjunct to Levodopa Therapy in Patients With Parkinson Disease and Motor Fluctuations: A Randomized Clinical Trial. *JAMA Neurol.* 2017 Feb 1;74(2):197-206.

Importance: Catechol O-methyltransferase (COMT) inhibitors are an established treatment for end-of-dose motor fluctuations associated with levodopa therapy in patients with Parkinson disease (PD). Current COMT inhibitors carry a high risk for toxic effects to hepatic cells or show moderate improvement. Opicapone was designed to be effective without the adverse effects. Objective: To evaluate the efficacy and safety of 25- and 50-mg/d dosages of opicapone compared with placebo as adjunct to levodopa therapy in patients with PD experiencing end-of-dose motor fluctuations. Design: This phase 3 international, multicenter outpatient study evaluated a 25- and a 50-mg/d dosage of opicapone in a randomized, double-blind, 14- to 15-week, placebo-controlled clinical trial, followed by a 1-year open-label phase during which all patients received active treatment with opicapone. Patients with PD who experienced signs of end-of-dose deterioration and had a mean total awake off-time (state of akinesia or decreased mobility) of at least 1.5 hours, not including morning akinesia, were enrolled. Data were collected from March 18, 2011, through June 25, 2013. Data from the evaluable population were analyzed from July 31, 2013, to July 31, 2014. Main Outcomes and Measures: The primary efficacy outcome of the double-blind phase was the change from baseline in absolute off-time vs placebo based on patient diaries. The open-label phase focused on maintenance of treatment effect in off-time. Results: A total of 427 patients (258 men [60.4%] and 169 women [39.6%]; mean [SD] age, 63.1 [8.8] years) were randomized to a 25-mg/d (n = 129) or a 50-mg/d (n = 154) dosage of opicapone or to placebo (n = 144). Of these, 376 patients completed the double-blind phase and entered the open-label phase, of whom 286 completed 1 year of open-label treatment. At the end of the double-blind phase, the least squares mean change (SE) in off-time was -64.5 (14.4) minutes for the placebo group, -101.7 (14.9) minutes for the 25-mg/d opicapone group, and -118.8 (13.8) minutes for the 50-mg/d opicapone group. The adjusted treatment difference vs placebo was significant for the 50-mg/d opicapone group (treatment effect, -54.3 [95% CI, -96.2 to -12.4] minutes; P = .008), but not for the 25-mg/d opicapone group (treatment effect, -37.2 [95% CI, -80.8 to

6.4] minutes; P = .11). The off-time reduction was sustained throughout the open-label phase (-126.3 minutes at 1-year open-label end point). The most common adverse events in the opicapone vs placebo groups were dyskinesia, constipation, and dry mouth. Fifty-one patients (11.9%) discontinued from the study during the double-blind phase. Conclusions and Relevance: Treatment with a 50-mg once-daily dose of opicapone was associated with a significant reduction in mean daily off-time in levodopa-treated patients with PD and motor fluctuations, and this effect is maintained for at least 1 year. Opicapone was safe and well tolerated.



- Margolesky J, Singer C. Extended-release oral capsule of carbidopa-levodopa in Parkinson disease. *Ther Adv Neurol Disord*. 2017 Oct 30;11:1756285617737728.

Motor fluctuations complicate the treatment of patients with Parkinson's disease receiving levodopa. Extended-release carbidopa-levodopa has a pharmacokinetic profile that provides a more continuous levodopa serum concentration. Patients taking this formulation can expect longer duration of action and fewer doses per day, similar clinical improvement when compared to other levodopa formulations, and with a theoretically lower risk of developing motor fluctuations. Several studies, including three randomized control trials provide evidence for the efficacy, safety and tolerability of extended release carbidopa-levodopa in patients with both early and advanced Parkinson's disease are reviewed here. Also provided is guidance for dosing of and conversion to extended release carbidopa-levodopa as well as a discussion of its place in the clinical practice.



- Müller T, Möhr JD. Long-term management of Parkinson's disease using levodopa combinations. *Expert Opin Pharmacother*. 2018 Jun 18:1-9. doi: 10.1080/14656566.2018.1484108. [Epub ahead of print]

Parkinson's disease is a chronic, neurodegenerative disease. Its symptoms and course are heterogeneous. After several years of investigative drug studies, levodopa remains the most efficacious drug despite its long-term limitations. Consequently, research into new drug delivery modes is ongoing. Areas covered: This review summarizes past and current advances of levodopa therapy with a focus on long-term patient management. Current research aims to increase drug bioavailability and to deliver it to the brain continuously. Reduced fluctuations improve drug efficacy and levodopa-associated motor complications. Less considered metabolic long-term consequences of levodopa are impaired methylation capacity and antioxidant defense. Both may contribute to disease progression and weaken physiological available human neuronal repair mechanisms. Expert opinion: New developed formulations will improve pharmacokinetic and pharmacodynamic behavior. The authors suggest the regular supplementation with methyl group-donating and free radical scavenging substrates to weaken the metabolic consequences of chronic and high levodopa dosing. Many patients perform this nutrient supplementation in their diet already.



- Pirio Richardson S, Wegele AR, Skipper B, Deligtisch A, Jinnah HA; Dystonia Coalition Investigators. Dystonia treatment: Patterns of medication use in an international cohort. *Neurology*. 2017 Feb 7;88(6):543-550.

OBJECTIVE: To determine the frequency of medication use in patients with dystonia enrolled in an international biorepository study. METHODS: In a cross-sectional analysis, we included 2,026 participants enrolled at 37 sites in the United States, Canada, Europe, and Australia through Project 1 of the Dystonia Coalition, an international biorepository study. The primary aim was to assess the frequency of medication classes recommended for treating patients with dystonia, and the secondary aim was to compare characteristics (disease type, age, sex, duration of disease, comorbid conditions, severity). RESULTS: Querying the database for the presence of any medication for dystonia used (includes both injectable and oral therapy), we found 73% using medications (n = 1,488) and 27% using no dystonia medications (n = 538). Furthermore, 61% of the total sample used botulinum toxin (BoNT) therapy alone or in combination. Differences were found in medication use patterns by dystonia type, with the lowest oral medication use in focal dystonia and highest use in generalized dystonia; by region, with highest BoNT therapy rate reported in Italy and the lowest in the Northeast region of the United States; and by focal dystonia subtype, with highest BoNT therapy alone in blepharospasm and spasmodic dysphonia (49%) and lowest in other cranial dystonia (32%). CONCLUSIONS: The majority of patients with dystonia enrolled in the Dystonia Coalition Project 1 were using medications to treat their dystonia. Overall, a complex picture of medication use patterns emerged,

with factors such as region, disease duration, type of dystonia, disease severity, and psychiatric comorbidities all playing a significant role. © American Academy of Neurology.



- Schapira AH, Fox SH, Hauser RA, Jankovic J, Jost WH, Kenney C, Kulisevsky J, Pahwa R, Poewe W, Anand R. Assessment of Safety and Efficacy of Safinamide as a Levodopa Adjunct in Patients With Parkinson Disease and Motor Fluctuations: A Randomized Clinical Trial. *JAMA Neurol.* 2017 Feb 1;74(2):216-224.

Importance: Although levodopa remains the most effective oral pharmacotherapy for Parkinson disease (PD), its use is often limited by wearing off effect and dyskinesias. Management of such complications continues to be a significant challenge. Objective: To investigate the efficacy and safety of safinamide (an oral aminoamide derivative with dopaminergic and nondopaminergic actions) in levodopa-treated patients with motor fluctuations. Design, Setting, and Participants: From March 5, 2009, through February 23, 2012, patients from academic PD care centers were randomized (1:1 ratio) to receive double-blind adjunctive safinamide or placebo for 24 weeks. All patients had idiopathic PD with "off" time (time when medication effect has worn off and parkinsonian features, including bradykinesia and rigidity, return) of greater than 1.5 hours per day (excluding morning akinesia). Their pharmacotherapy included oral levodopa plus benserazide or carbidopa in a regimen that had been stable for 4 weeks or longer. During screening, each patient's regimen was optimized to minimize motor fluctuations. Study eligibility required that after 4 weeks of optimized treatment, the patients still have more than 1.5 hours per day of off time. Adverse events caused the premature study discontinuation of 12 individuals (4.4%) in the safinamide group and 10 individuals (3.6%) in the placebo group. Interventions: Patients took safinamide or placebo as 1 tablet daily with breakfast. If no tolerability issues arose by day 14, the starting dose, 50 mg, was increased to 100 mg. Main Outcomes and Measures: The prespecified primary outcome was each treatment group's mean change from baseline to week 24 (or last "on" treatment value) in daily "on" time (relief of parkinsonian motor features) without troublesome dyskinesia, as assessed from diary data. Results: At 119 centers, 549 patients were randomized (mean [SD] age, 61.9 [9.0] years; 334 male [60.8%] and 371 white [67.6%]): 274 to safinamide and 275 to placebo. Among them, 245 (89.4%) receiving safinamide and 241 (87.6%) receiving placebo completed the study. Mean (SD) change in daily on time without troublesome dyskinesia was +1.42 (2.80) hours for safinamide, from a baseline of 9.30 (2.41) hours, vs +0.57 (2.47) hours for placebo, from a baseline of 9.06 (2.50) hours (least-squares mean difference, 0.96 hour; 95% CI, 0.56-1.37 hours;  $P < .001$ , analysis of covariance). The most frequently reported adverse event was dyskinesia (in 40 [14.6%] vs 15 [5.5%] and as a severe event in 5 [1.8%] vs 1 [0.4%]). Conclusions and Relevance: The outcomes of this trial support safinamide as an effective adjunct to levodopa in patients with PD and motor fluctuations to improve on time without troublesome dyskinesia and reduce wearing off.



- Termsarasab P, Thammongkolchai T, Frucht SJ. Medical treatment of dystonia. *J Clin Mov Disord.* 2016 Dec 19;3:19.

Therapeutic strategies in dystonia have evolved considerably in the past few decades. Three major treatment modalities include oral medications, botulinum toxin injections and surgical therapies, particularly deep brain stimulation. Although there has been a tremendous interest in the later two modalities, there are relatively few recent reviews of oral treatment. We review the medical treatment of dystonia, focusing on three major neurotransmitter systems: cholinergic, GABAergic and dopaminergic. We also provide a practical guide to medication selection, therapeutic strategy and unmet needs.



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*Next Month's Issue:*

Improving Mobility/Disability Through Pain Management

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