흔히 보는 이상운동질환의 약물 치료

성 영 희
가천대학교 의과대학 신경과학교실

Tremor

Tremor Definition

- Tremor is the most common involuntary movement disorder
- Tremor can be defined as an **involuntary, rhythmic, periodic, mechanical oscillation of a body part.**
- Accurate diagnosis of tremor is important because appropriate treatment depends on the accuracy of the clinical diagnosis.

Clinical Assessment of Tremor

- **Topography**
  - Head
  - Chin
  - Jaw
  - Upper/lower extremity
  - Trunk
- **Activation condition**
  - Rest
  - Posture
  - Specific tasks
- **Frequency**
  - low <4 HZ
  - medium 4-7 Hz
  - high >7 Hz
- **Amplitude**

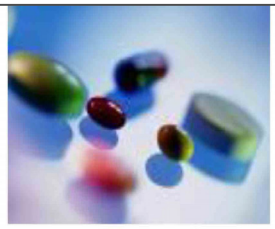
Clinical Assessment of Tremor

- Medical history should include details of tremor onset, family history, alcohol sensitivity, associated diseases, medications, and drug use/abuse.
- The general neurological exam is very important and has a great impact on the differential diagnosis.
- Clinical situation should guide additional workup (labs, imaging, etc…)

Enhanced Physiological tremor

- Physiological tremor is present in every normal subject with posture and action.
  - Strong emotion (such as anxiety or fear), physical exhaustion, hypoglycemia, hyperthyroidism, heavy metal poisoning, stimulants, alcohol withdrawal, caffeine, or fever.
- Enhanced physiological tremor is a visible, predominantly postural, and high frequency tremor of short duration (<2 years). Evidence for neurological disease related to the tremor must be excluded.
  - Hyperthyroidism, hypoglycemia
  - Drugs (TCAs, Lithium, bronchodilators, cocaine, alcohol,...)

Drug-induced Tremor



- Neuroleptics (haloperidol)
- GI motility agent (metoclopramide, levopride)
- Antiepileptics (especially VPA)
- Antidepressants
- Steroids
- Antiarrhythmics (especially amiodarone)
- Cyclosporine
- Cytostatics (e.g. vincristine)

Classical essential tremor (ET)

- Predominantly posture and action tremor that is usually slowly progressive over time. Rarely, resting tremors can also occur.
- Mean onset between 35-45 years of age.
- Prevalence rates vary from 0.4-5.6%.
- AD in 60%
- 50-90% improve with alcohol ingestion.
- Topography: hand>head>voice>leg>jaw>trunk/face

Archimedes Spiral

Left hand
Physician rating _____

Right hand
Physician rating _____

Severity:
0-none
1-mild
2-moderate
3-severe
4-incapacitating

Line Drawing

R •

•

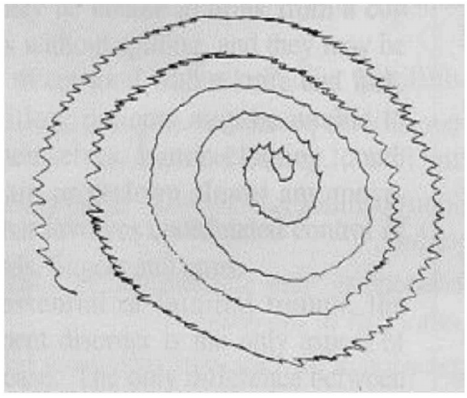
L •

•

Left hand
Physician rating _____

Right hand
Physician rating _____

Handwriting Sample



Treatment of Essential Tremor

- Mild tremor, which produces no functional or psychological disability/handicap and does not require treatment
- Mild to moderate tremor-producing disability only where there is tremor exacerbation in stressful situations such as social occasions or public speaking. These patients can be treated intermittently as necessary for these occasions.
- ET cases with persistent disability/handicap because of tremor. These patients need continued therapy to improve daily life function.
- ET cases that have persistent handicap but whose tremor persists despite appropriate pharmacotherapy. Alternatives to conventional pharmacotherapy should be considered in these cases.

Primidone

- Drug with established efficancy (level A)

- Anticonvulsant of the barbiturate class
- 6 double-blind placebo-controlled studies
- Estimated percentage reduction in tremor amplitude of 60% (range 42-76%)
- Side effects : dizziness, drowsiness, disequilibrium
  - 500mg 이상시 대부분의 환자에서 나타남
  - Acute toxic reaction-common : start on very low dose 25
  - Total daily dose 150mg 이하 권고
- 대웅 프리미돈 250mg _ 0.25T HS → 0.5T HS

Propranolol

-Drug with established efficancy (level A)

- Non-selective beta adrenergic blocker
- 13 double-blind placebo-controlled studies.
- 54.1% improvement (range 32-75%), measured with accelerometry
- 50% of patients have lasting benefit, with tolerance developing in about 14%
- Side effect : bradycardia, syncope, fatigue, erectile dysfunction
- Begin with 30-60mg/day → 60-240mg/day

Drug with probable efficancy (level B)

	Number of patients	Mean or median daily dose	Mean improvement in clinical rating (maximum possible score)	Estimated improvement in tremor amplitude (%)	Improvement measured by accelerometry (%)
Atenolol					
Jefferson et al[66]	9	50–100 mg	2·6 (25)	38%	..
Larsen et al[67]	24	100 mg	..	..	37%
Leigh et al[77]	24	100 mg	1·8 (30)	24%	..
Sotalol					
Jefferson et al[66]	9	80–240 mg	3·8 (25)	51%	..
Leigh et al[77]	24	160 mg	2·2 (30)	29%	..
Alprazolam					
Gunal et al[54]	22	1·5 mg	2 (14)	48%	..
Huber and Paulson[78]	24	0·75 mg	0·79 (4)	60%	..
Topiramate					
Connor[79]	24	333 mg	1·38 (12)	41%	..
Connor et al[80]	62	215 mg	6·2 (84)	29%	..
Ondo et al[81]	208	292 mg	10·8 (100)	39%	..
Frima and Grunewald[82]	13	100 mg	NS	NS	NS
Gabapentin monotherapy					
Gironell et al[83]	16	1200 mg	8·06 (76)	39%	77%

..=not done. NS=not significant.

CME

Topiramate in essential tremor

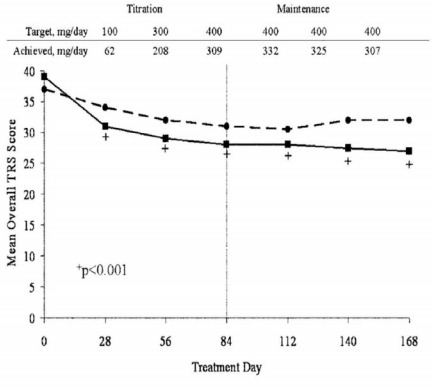
A double-blind, placebo-controlled trial

W.G. Ondo, MD; J. Jankovic, MD; G.S. Connor, MD; R. Pahwa, MD; R. Elble, MD, PhD; M.A. Stacy, MD; W.C. Koller, MD, PhD†; L. Schwarzman, MBA; S.-C. Wu, PhD; and J.F Hulihan, MD, on behalf of the Topiramate Essential Tremor Study Investigators*

Table 2 *Tremor Rating Scale scores*

	Topiramate, n = 108, mean (SD)	Placebo, n = 100, mean (SD)	*p* Value*
Overall tremor rating			
Baseline	38.7 (12.4)	37.3 (12.0)	
Mean change	−10.8 (9.5)	−5.8 (7.5)	0.001
Percent change	−28.8 (24.7)	−16.0 (21.6)	0.001
Upper limb tremor severity			
Baseline	45.3 (12.2)	44.4 (13.8)	
Mean change	−12.7 (14.8)	−8.9 (13.2)	0.06
Percent change	−28.1 (32.9)	−21.0 (31.1)	0.111
Specific motor tasks/function			
Baseline	39.7 (17.0)	38.6 (15.6)	
Mean change	−10.3 (12.6)	−4.9 (9.5)	<0.001
Percent change	−23.7 (31.1)	−11.6 (28.0)	0.002
Functional disability			
Baseline	31.3 (15.7)	29.0 (14.0)	
Mean change	−9.4 (13.3)	−3.7 (8.8)	0.001
Percent change	−28.0 (60.1)	−12.3 (37.9)	0.046

* Placebo vs topiramate; analysis of covariance of final score with baseline score as covariate.
† Placebo vs topiramate; least squares mean.



Topiramate

Common side effect

- Weight loss (mean :3.6kg)
- Anorexia
- Extremity paraesthesias
- Trouble concentrating
- Memory disturbance
- Increased risk of kidney stones

Table 3 *Most common adverse events* (safety evaluable)*

	Patients, %			
	Topiramate, n = 116		Placebo, n = 105	
	Total	Discontinuations	Total	Discontinuations
Paresthesia	28	5	5	0
Weight loss	22	1	3	0
Taste perversion	19	2	0	0
Upper respiratory tract infection	19	0	14	0
Fatigue	16	2	5	1
Nausea	16	3	7	0
Appetite decrease	14	2	3	0
Memory difficulty	13	1	1	0
Dizziness	13	1	11	1
Somnolence	12	3	6	1
Diarrhea	12	1	8	0
Headache	11	0	8	0

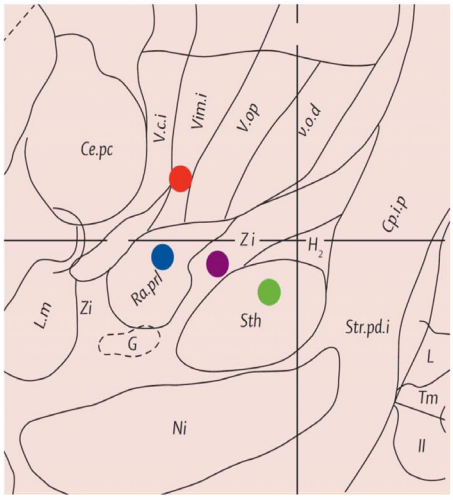
* Incidence of ≥10% in either treatment group; patients may report more than one adverse event.

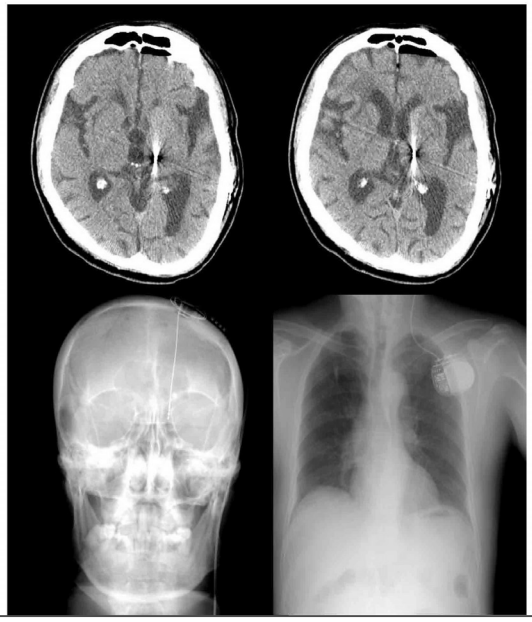
Recommendations for drugs with uncertain or no efficacy

- **Level C (possibly effective)**
  - Clonazepam, clozapine, nadolol, nimodipine, botulinum toxin
- **Level U (inadequate evidence to confirm or exclude efficacy)**
  - Clonidine, gabapentin (adjunct therapy), glutethimide, metoprolol, L-tryptophan/pyridoxine, nicardipine, octanol†, olanzapine, phenobarbital, pregabalin†, quetiapine, T2000†, theophylline, tiagabine†, sodium oxybate†, zonisamide†
- **Agents with recommendations against use (ineffective)**
  - Trazodone (level A), acetazolamide (level B), amantadine† (level B), carisbamate† (level B), isoniazid (level B), levetiracetam† (level B), pindolol (level B), 3,4-diaminopyridine† (level B), methazolamide (level C), mirtazapine (level C), nifedipine (level C), verapamil(level C)

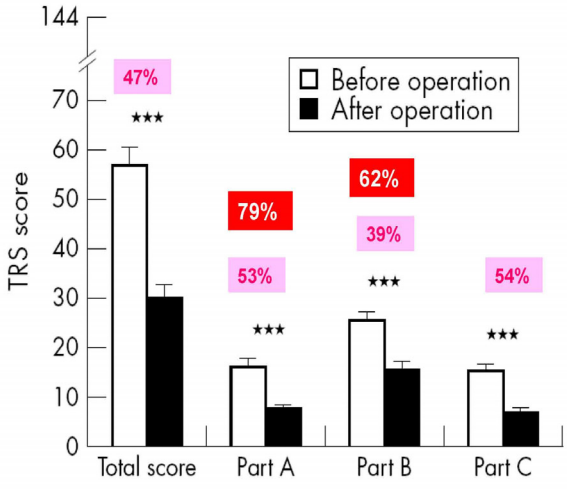
Stereotatic surgery

Targets for surgical treatment of essential tremor





Preoperative and postoperative scores of the Fahn-Tolosa-Marín tremor rating scale (TRS) *in 27 patients with essential tremor treated with thalamic DBS. Total mean score (SEM), as well as scores from the three subscales of TRS are shown. ***p<0.0001*



Treatment of head and voice tremor

- Isolated and predominant head and voice tremor
  - Variant of ET ~ forms of dystonia or separate entities ?
  - Suppression with sensory trick ~ dystonic tremor, not ET
- Level C recommendation
  - Propranolol
  - Botulinum toxin
  - DBS
- Level U recommendation
  - Primidone

Studies of treatment for head tremor

	Treatment	Study design	Number of patients	Mean baseline and follow-up head tremor scores (0–4)	Estimated improvement in tremor amplitude (%)*	Improvement measured by accelerometry (%)
Koller[142]	Propranolol 160–320 mg/day	DBPCC	9	2·44→0·89	71%	50%
Calzetti et al[72]	Propranolol 120 mg single oral dose	DBPCC	9	..	..	33%
Calzetti et al[72]	Propranolol 120 and 240 mg/day for 2 weeks	DBPCC	9	..	..	NS
Sasso et al[143]	Primidone (750 mg/day max)	DBPCC	6	..	..	NS
Sasso et al[143]	Phenobarbital (90 mg/day max)	DBPCC	6	..	..	NS
Pahwa et al[144]	Botulinum toxin type A	DBPCC	10	NS	..	NS
Wissel et al[18]	Botulinum toxin type A	UCS	14 ET 29 TCD	..	..	61% 49%
Koller et al[145]	Unilateral Vim DBS	Masked examiner	24	2·7→1·3	68%	..
Blomstedt et al[108]	Unilateral Vim DBS	UCS	19	1·5→0·6	82%	..
Obwegeser et al[146]	Unilateral Vim DBS	UCS	14	2·1→1·3	48%	..
Obwegeser et al[146]	Bilateral Vim DBS	UCS	13	2·1→0·1	80%	..
Ondo et al[147]	Unilateral Vim DBS	UCS	11	2·0→1·4	38%	..
Ondo et al[147]	Bilateral Vim DBS	UCS	11	2·0→0·7	65%	..
Sydow et al[115]	Unilateral Vim DBS	UCS	15	1·1→0·6	33%	..
Sydow et al[115]	Bilateral Vim DBS	UCS	4	2·0→0·3	75%	..
Taha et al[148]	Bilateral Vim DBS	UCS	10	Improvement† (%) >75% (n=5), >50% (n=4), and >25% (n=1)	..	..

Studies of treatment for voice tremor

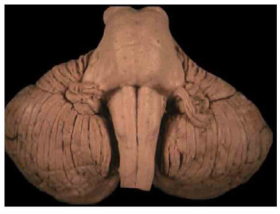
	Treatment	Study design	Number of patients	Mean baseline and follow-up voice tremor (0–4)	Improvement by acoustic analysis (%)
Koller et al[149]	Propranolol 80–320 mg/day	DBPCC	6	3·2→3·1	NS
Busenbark et al[150]	Methazolamide 25–300 mg/day	DBPCC	9	NS	NS
Adler et al[151]	Botulinum toxin type A	Masked examiner	13	2·41→1·51	27%
Warrick et al[152]	Botulinum toxin type A	Masked examiner	10	NS	NS
Blomstedt et al[108]	Unilateral Vim DBS	UCS	19	0·7→0·7	..
Carpenter et al[153]	Unilateral and bilateral Vim DBS	Masked examiner	7 (5 unilateral, 2 bilateral)	2·57→1·86	16·4%
Obwegeser et al[146]	Unilateral Vim DBS	UCS	14	1·8→1·3	..
Obwegeser et al[146]	Bilateral Vim DBS	UCS	13	1·4-1·8→0·3	..
Ondo et al[147]	Bilateral Vim DBS	Masked rater	11	1·2→0·5	..
Sydow et al[115]	Unilateral Vim DBS	UCS	15	0·4→0·3	..
Sydow et al[115]	Bilateral Vim DBS	UCS	4	1·0→0·4	..
Taha et al[148]	Bilateral Vim DBS	UCS	7	Improvement* >50% (n=6), >25% (n=1)	..

DBPCC=double-blind, placebo-controlled crossover. NS=not significant. DBS=deep brain stimulation. UCS=uncontrolled case series. ..=analysis not done. *Improvement (%) was estimated; tremor amplitude was not rated.

Parkinson's Disease

- Classic Parkinsonian tremor:
  - Rest tremor
  - Asymmetric
  - Temporarily suppressed with voluntary movement
  - Increased amplitude with mental stress, contralateral movements, and during gait
- Treat with anti-Parkinsonian agents and DBS in medically-refractory cases of tremor-predominant PD

Cerebellar Tremors



- Intention tremors
- Often unilateral
- Slow (<5 Hz)
- Postural tremor may be present but no rest tremor
- Medical treatments typically ineffective

Dystonic tremor

- Postural and kinetic tremor not usually seen during complete rest that occurs in a body part affected by dystonia.
- They are focal tremors with irregular amplitudes and variable frequencies.
- Geste antagoniste
- Botulinum toxin treatment of first choice
- DBS for medically-refractory cases

Restless leg syndrome

Restless legs

Karl-Axel Ekbom 1945

" .. A hitherto **overlooked** disease in the legs characterized by peculiar paresthesia.."

RLS

48.6% report discussing RLS Symptoms with doctor

7.1% diagnosed with RLS

93% of RLS missed by doctors

" **RLS is the most common disorder your doctor has never heard of"**

Reasons for under diagnosis of RLS

- Not known – Rare disorder
- Not distressing, patient fails to report symptoms
- Difficult to diagnosis
- No effective treatment

Restless Leg Syndrome

- *Ekbom's Syndrome, Focal Akathisia of the Legs*

- **Sensorimotor disorder**

- urge to move, usually a/c paresthesia
- occurs or worsens at rest & night, relieved by activity.

- Circadian rhythm, with maximum ocurring after midnight
- Major impact on nocturnal sleep and daytime functioning
- a/c medical condition : uremia, anemia, various neuropathies
- Familial aggregation; - 50%>, - autosomal dominant fashion
- - RLS susceptibility genes on chromosome 12q and 14q
- Brain iron deficiency

Straightforward diagnosis of RLS

How does it feel?	**Criterion 1:** An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs
What brings it on?	**Criterion 2:** The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying or sitting
What relieves it?	**Criterion 3:** The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues
When does it occur?	**Criterion 4:** The urge to move or unpleasant sensations are worse in the evening or night than during the day, or only occur in the evening or night

Diagnostic Criteria of RLS

Table 1. Revised International Restless Legs Syndrome Study Group (IRLSSG) diagnostic criteria (2012)

Essential diagnostic criteria (all must be met)
1. Urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable or unpleasant sensation in the legs
2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during period of rest or inactivity
3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally removed by movement
4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night
5. Above features are not solely account for as symptoms primary to another medical or a behavioral condition (e.g. myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping etc.)
Specifiers for clinical course of RLS
A. Chronic persistent RLS: >2/wk
B. Intermittent RLS: <2/wk but at least 5 life time events
Specifiers for clinical significance of RLS
The symptoms of RLS cause distress or impairment in social, occupational, educational or other important areas of functionality by the impact on sleep, energy/vitality, daily activities, behavior, cognition or mood.

RLS, restless legs syndrome.

Etiology

- **Primary (a genetic predisposition?)**
  - up to 60% report a positive family history.
  - autosomal dominant mode of inheritance with variable expressivity,
  - possible anticipation.
  - one twin study showing a high concordance rate (83.3%)

- **Secondary**
  - iron deficiency (31%)
  - pregnancy (20%)
  - end-stage renal disease (20-65%)
  - Neuropathy (5.2% ,underestimated)
  - Rhematoid arthritis (25%)
  - Parkinson's disease (20%)
  - MS etc
  - Spinocerebellar Ataxia: more common in the various forms of spinocerebellar ataxia, particularly SCA-3
  - Charcot-Marie Tooth (CMT):in 37% of CMT2, none of CMT1
  - Psychiatric Disease: depression, anxiety and symptoms of Attention-Deficit-Hyperactivity Disorder (ADHD)
  - Hypertension and Heart Disease: much more likely to have hypertension (O.R. 1.5) and heart disease (O.R. 2.5)
  - Medication: antipsychotic agents(Neuroleptic -Induced Akathisia)

Antidepressants (eg, amitriptyline, paroxetine)

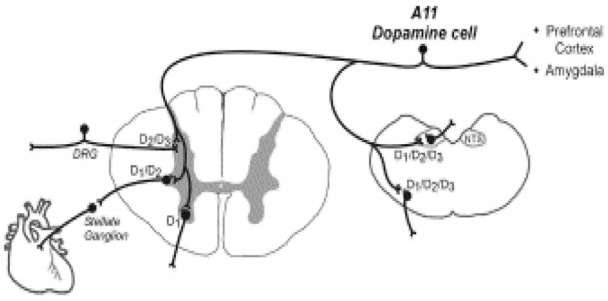
Supportive Clinical Features of RLS

- **Positive Family History of RLS**
- **Improvement with dopaminergic therapy**
- **Periodic Limb Movements in Sleep (PLMS)**

- Periodic limb movements in sleep (PLMS) occur in at least 85% of people with RLS; however, PLMS also commonly occur in other disorders and in the elderly. In children, PLMS are much less common than in adults

Pathophysiology of RLS/PLM

- Iron – CNS DA deficiency
- Dopamine diencephalospinal pathway lesions can induce RLS/PLM



Early and Late onset of RLS symptoms

• Early onset <=45,	Late onset > 45
• Slowly progressive	Rapidly progressive
• Family	Sporadic
• Primary	Secondary/primary
• Less affected by Ferritin	Strongly affected by Ferritin

Laboratoty study

- Clinical diagnostic questionnaire
- BUN, creatinine
- Fasting blood glucose, glucose tolerance test
- Iron, Ferritin, magnesium, thyroid-stimulating hormone (TSH), vitamin B-12, and folate
- CBC count

Nonpharmacologic Tx

- **Alleviate any underlying disease & conditions**
- **Iron Treatment**

Iron replacement theraphy is recommended for RLS patients who have a serum ferritin level of **<50mcg/L**

Nonpharmacologic Tx

- **Improve sleep hygine**
- **Exercise, Massage, TENS,**
- **Avoid substance**
  - Nicotine, caffeine, alcohol,
  - TCA, SSRI; intensify
  - Anti-histamines
  - Dopamine Rc blocker such as anti-nausea drugs (Macperan), neuroleptics
  - β blockers, some anticonvulsants, and lithium

RLS Treatment

- Dopamine Agonist
- Carbidopa/Levodopa
- Opioids
- Benzodiazepines
- Anticonvulsants
- Behavioral Treatments
- Iron Treament

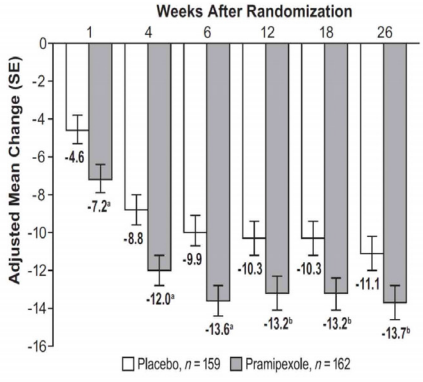
Treatment Protocol

- Caffeine restriction, sleep hygiene control
- Intense pain : gabapentin
- Most patients: low dose dopamine agonist
- Pregnant women: mild opioid
- With Depression : Try to avoid antidepressant except Wellbutrin

Dopamine agonist_Pramipexole

Efficacy and augmentation during 6 months of double-blind pramipexole for restless legs syndrome

Background: Pramipexole is an effective treatment for restless legs syndrome (RLS), but no controlled studies have lasted >12 weeks.
Methods: RLS patients (N = 331) with pretreatment serum ferritin >30 ng/mL were randomly assigned to take double-blind optimized pramipexole (0.125–0.75 mg/d) or placebo for 26 weeks. The primary efficacy endpoint was change in International RLS Study Group Rating Scale (IRLS) score. Other endpoints assessed global change, symptoms, and QoL. Patients maintained symptom diaries. Cases meeting predefined criteria for suspected augmentation were reviewed by a blinded expert panel, which used a predefined algorithm.
Results: Among 321 patients providing post-baseline data, of whom 234 completed 26 weeks, pramipexole was more effective than placebo by multiple endpoints, including an adjusted mean IRLS score change of −13.7 vs. −11.1 (p = 0.0077) and an IRLS responder rate (⩾50% score reduction) of 58.6% vs. 42.8% (p = 0.0044). Efficacy showed considerable country-to-country variability. Six-Month incidence of confirmed augmentation was 9.2% for pramipexole and 6.0% for placebo. The rate increased with treatment duration for pramipexole but not placebo. Treatment-related adverse events (AEs) were more likely for pramipexole than for placebo, but discontinuation due to AEs was less likely.
Conclusions: During a 6-month period, pramipexole was effective, safe, and generally well tolerated. Because risk of augmentation may have increased over 6 months, it should be studied in longer trials. Beginning or mild augmentation is difficult to distinguish from natural RLS fluctuation, at least in a non-iron-deficient population.

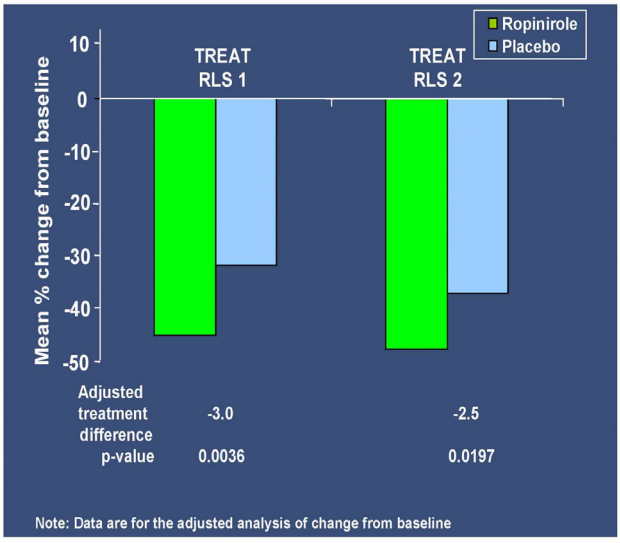


Dopamine agonist_Pramipexole

- Pramipexole is probably effective for one year on the basis of class II evidence (no placebo in long term phase) from a 52 week, double blind, randomised controlled study in 719 patients (0.25 and 0.5 mg/day), which reported a change in IRLS score compared with placebo of −0.6 (pramipexole 0.25) and −3.2 (pramipexole 0.5) (both P<0.05).

- Side effect : fatigue, sommolence, nausea, insomnia, headache, nasopharyngitis, muscle spasm, arthralgia

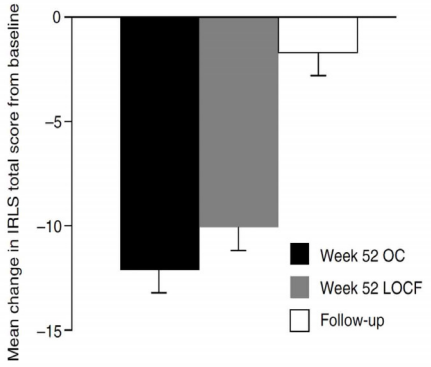
Dopamine agonist_Ropinirole



1. Trenkwalder C et al. J Neurol Neurosurg Psychiatry 2004; 75: 92–7.
2. Walters A et al. (Data on file GSK, Study 194.)

Dopamine agonist_Ropinirole

A 52-week open-label study of the long-term safety of ropinirole in patients with restless legs syndrome



Most common (≥10%) adverse events and most common (≥5%) adverse events considered related or possibly related to study drug during the open-label treatment phase in the safety population

Preferred term	All adverse events ($n = 309$)	Adverse events in weeks 0–12	Adverse events related to treatment
Any AE	282 (91.3)	185 (59.9)	172 (55.2)
Nausea	115 (37.2)	95 (30.7)	98 (31.7)
Headache	59 (19.1)	45 (14.6)	19 (6.1)
Arthralgia	41 (13.3)	10 (3.2)	1 (0.3)
Nasopharyngitis	37 (12.0)	22 (7.1)	0 (0)
Dizziness	35 (11.3)	22 (7.1)	20 (6.5)
Back pain	34 (11.0)	17 (5.5)	1 (0.3)
Vomiting	32 (10.4)	24 (7.8)	22 (7.1)
RLS	28 (9.1)	7 (2.3)	26 (8.4)
Fatigue	26 (8.4)	20 (6.5)	19 (6.1)
Somnolence	22 (7.1)	18 (5.8)	19 (6.1)

Dopamine agonist_Ropinirole

Systematic Evaluation of Augmentation during Treatment with Ropinirole in Restless Legs Syndrome (Willis-Ekbom Disease): Results from a Prospective, Multicenter Study over 66 Weeks

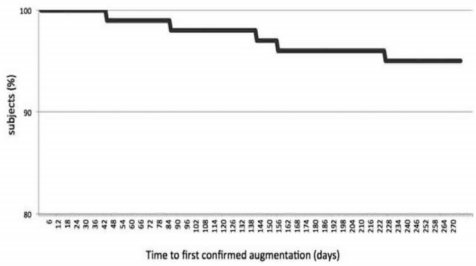


FIG. 3. Kaplan–Meier curve for time to first confirmed augmentation during first open-label phase.

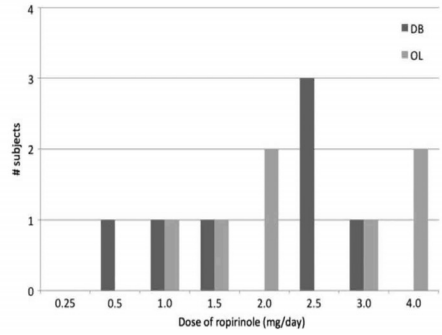


FIG. 4. Number of subjects with confirmed augmentation by dose of ropinirole.

Dopamine agonist

Suggested initial dose and maximum recommended dose for dopamine agonists

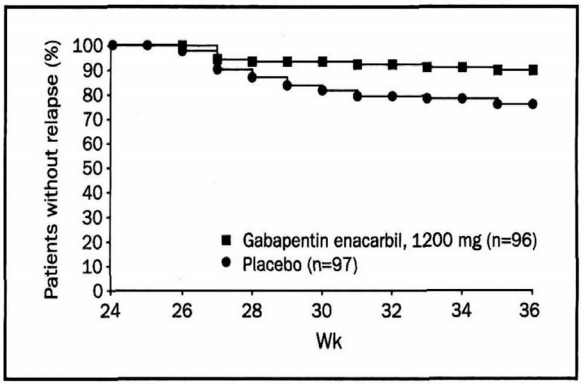
	Initial dose	Max. recommended dose
Pramipexole	0.125 mg/day	0.75 mg/day
Ropinirole	0.25 mg/day	4 mg/day
Rotigotine	1 mg/day	3 mg/day

Suggested initial dose for switching dopamine agonists

	Rotigotine	Pramipexole ER*
Pramipexole		
0.25 mg	2 mg	0.375 mg
0.50 mg (or higher)	3 mg	0.75 mg
Ropinirole		
0.5–1.0 mg	2 mg	0.375 mg
2 mg or higher	3 mg	0.75 mg

a2d ligand_Gabapentin enacarbil

- Improvement in symptom severity at doses between 600 and 1200 mg per day.



Adverse event	Single-blind phase Gabapentin enacarbil, 1200 mg (n=326)			
	Mild	Moderate	Severe	Total
Any adverse event	93 (28.5)	142 (43.6)	29 (8.9)	264 (81.0)
Somnolence	60 (18.4)	31 (9.5)	6 (1.8)	97 (29.8)
Dizziness	50 (15.3)	21 (6.4)	1 (0.3)	72 (22.1)
Headache	21 (6.4)	15 (4.6)	5 (1.5)	41 (12.6)
Nasopharyngitis	22 (6.7)	7 (2.2)	0	29 (8.9)
Nausea	12 (3.7)	9 (2.8)	0	21 (6.4)
Viral gastroenteritis	3 (0.9)	5 (1.5)	1 (0.3)	9 (2.8)

a2d ligand_Pregabalin

- At a dose of 150-450 mg/day, pregabalin is considered effective for the treatment of RLS/WED.
- One randomised, double blind study that evaluated the efficacy of pregabalin and the incidence of augmentation over 52 weeks in 719 patients.
  - Pregabalin significantly reduced the IRLS score compared with pramipexole at 52 weeks (−3.8 and−3.1, respectively; P<0.001).
  - The rate of augmentation over a period of 40 or 52 weeks was significantly lower with pregabalin than with pramipexole at a dose of 0.5mg (2.1% *v* 7.7%; P=0.001) but not at a dose of 0.25 mg(2.1% *v* 5.3%; P=0.08).

a2d ligand

	Starting dose		Usual effective daily dose
	<65 years	>65 years	
α2δ ligands			
Approved (USA, Japan as of 2015)			
Gabapentin enacarbil	600 mg	300 mg	600–1200 mg
Not approved			
Pregabalin	75 mg	50 mg	150–450 mg
Gabapentin*	300 mg	100 mg	900–2400 mg

Opiates

- **Oxycodone extended release**
  - Prolonged release oxycodone-naloxone (5.0 mg/2.5 mg twice daily uptitrated to a maximum dose of 40 mg/20 mg twice daily)
- **Methadone**
  - mean 15.5 mg/day

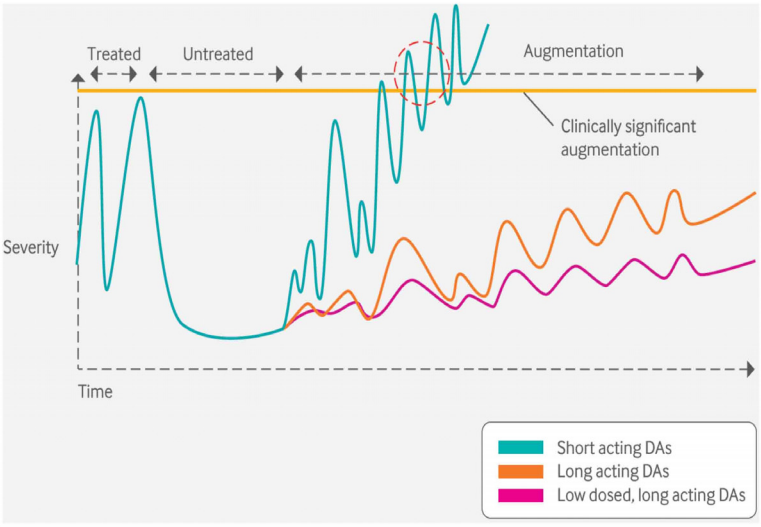
Others

- **Tetrabenazine**
  - mild if any benefit in the use of tetrabenazine in the treatment of RLS/WED in patients with comorbid hyperkinetic movement disorders
- **Clonazepam**
  - One Class IV study included 34 patients with RLS/WED or periodic limb movement disorder treated with clonazepam for at least 6 months with a mean initial dose of 0.9 mg, which increased to 1.35 mg.

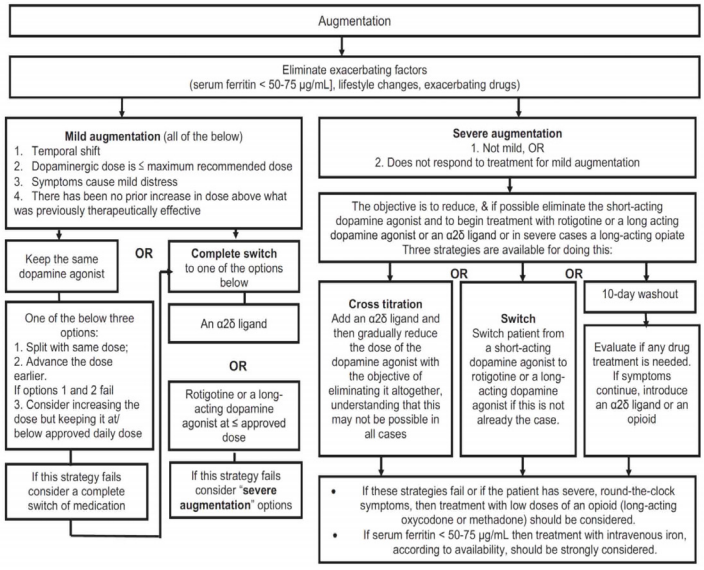
Clinical consensus of the benefits and risks for each pharmacologic treatment of RLS/WED

	Levodopa	Nonergot DA		Ergot-based DA	$\alpha_2\delta$ Ligand	Opioid	Clonazepam
		Short-acting	Long-acting				
The potential of the drug to cause the following adverse events							
Augmentation	+++	++	+	++	0	NK	0
LoE	+++	++	NK	++	+	+	NK
ICD	0	+	0/+	NK	0	0	0
EDS	NK	++	+	++	+++	+	++
Negative mood	0	0	0	0	+	+	++
Weight gain	0	0	0	0	++	0	0
General toxicity	+	+	++	+++	+	++	+
The potential of the drug to have positive effect on these parameters							
Subjective nighttime sleep	0	+	+	+	++	++	++
Classic nighttime RLS/WED symptoms	+	++	++	++	++	++	0
QoL	NK	++	++	++	++	NK	NK
Pain reduction	+	+	+	+	++	+++	0

Therapeutic response during treatment with dopamine agonists



Augmentation treatment algorithm



Blepharospasm & Hemifacial spasm

Introduction

- Blepharospasm
  - Focal dystonia
  - Spasm of the orbicularis oculi (OO) muscles.
  - Excessive involuntary closure of the eyelids.
    - → Failure of levator contraction
    - → Apraxia of lid opening
      or motor persistence of the OO muscles

Introduction

- Primary blepharospasm
  - Benign essential blepharospasm(BEB)
  - Not associated with any known etiology
- Secondary blepharospasm
  - Identifiable neurologic or ophthalmologic disorder or documented pathologic lesion.
  - Lesions associated with blepharospasm have been documented in the basal ganglia, brainstem, and thalamus, and more recent case reports confirm this.

Introduction

- Types of blepharospasm
  - Increased rate of blinking
  - Prolonged lid closure
  - Strong lid force
  - Difficult lid opening (lid opening inhibition type)
  - Combination of the above
  - Blepharospams consistent with Meige's syndrome

Introduction

- Hemifacial spasm (HFS)
  - nondystonic hyperkinetic movement disorder characterized by intermittent brief tonic or clonic contraction of the muscles of facial expression
  - Unilateral ; bilateral HFS in fewer than 2%
  - Primary HFS (79%) : compression of facial nerve at the root exit zone in the brainstem, usually by an ectatic artery
  - Secondary HFS (21%) : brainstem or facial nerve damage from bell's palsy, trauma, tumor, infection, or demyelinating disorder

Treatment

- Drug therapy
  - ~ not been generally successful
  1. Anticholinergic drug
  2. GABAergic compound such as baclofen and clonazepam
  3. Anti-dopaminergic agent such as tetrabenazine
  4. cyproheptadine, carbamazepine and tricyclic antidepressant
  5. dopaminergic agent

- Benign Essential Blepharospasm Research Foundation
  1162/1653 pt (70%) ~ tried oral therapy
  → **43% : improvement**
    - 52% : less than 50% improvement
    - 22% : 50%~75% improvement
    - 14% : 75%~90% improvement
    - 12% : 90% improvement

Treatment

- Botulinum toxin
  - ~ first choice of therapy

- Late failure
  - Antibody production
  - Excessive sprouting of motor neurons

Treatment

Table 1 Muscles commonly involved in blepharospasm

Muscle	Action
Orbicularis oculi	Close eyes
Corrugator supercilii	Draws eyebrows down and nasally
Procerus	Pulls forehead and skin between eyebrows down

Table 3 Muscles commonly involved in hemifacial spasm

Muscle	Action
Orbicularis oculi	Closes eyes
Corrugator supercilii	Draws eyebrows down and nasally
Zygomaticus major	Elevates and draws angle of mouth upward
Zygomaticus minor	Raises and draws upper lip laterally
Levator labii superioris alaeque nasi	Raises upper lip and flares nostril
Risorius	Draws angle of mouth laterally
Orbicularis oris	Closes and puckers the lips
Mentalis	Raises skin over chin
Depressor anguli oris	Depresses angle of the mouth
Platysma	Wrinkles the skin of the lower face and neck

Treatment

- Botulinum toxin: evidence-based medicine criteria in blepharospasm and hemifacial spasm
  - 55 open case-control studies with more than 2500 patients
    - The success rate : 90%
  - five double-blind studies with 80 patients
    - Good to excellent improvement : 66% ~ 98.6%
    - The mean duration of action : 2 ~ 3.5 months
  - Side effect
    - Dry eye (M/C) : 7.5%
    - Ptosis : 2.8% ~12%
    - Mild facial weakness : 8.5%
    - Diplopia : 1% ~13%
    - All of these undesired effects were transitory, and no systemic effect was seen in any study.

Treatment

- **Doxorubicin chemomyectomy**
  - Eighteen patients with blepharospasm / nine patients with hemifacial spasm
  - Doxorubicin chemomyectomy is an evolving technique and an effective treatment for essential blepharospasm and hemifacial spasms symptomatically localized to the eyelids.
  - Sixteen (59%) of the initial series of 27 patients completed the treatment.
  - Skin side effects that have limited its acceptance.
- A liposome encapsulated form of the drug that limits skin side effectsis in clinical trial.
- Oral agents work only weakly and cannot be depended on.

Treatment

- **Myectomy operation for Blepharospasm**
  - Most cases that are refractory to botulinum toxin have eyelid deformities associated with blepharospasm or associated apraxia of lid opening.
  - The OO and corrugator superciliaris muscles are removed to relieve spasms
  - The levator aponeurosis is tightened to help elevate the eyelids, and in rare cases of severe apraxia of lid opening a frontalis suspension may be required.

Treatment

- **Tinted lenses (FL-41) for Blepharospasm**
  - Reduce the light sensitivity associated with BEB
  - Originally described in Birmingham, for use in children with migraine headaches.
    - reduced migraines by one-half after 4 months of wear.
  - About 70% of patients have reported an improvement in blepharospasm (Digre,personal communication, 2000).
  - More work needs to be done in this area.

Treatment

- **Microvascular decompression for Hemifacial spasm**
  - 782 microvascular decompression procedures
    - 84% had excellent results and 7% had partial success 10 years postoperatively
    - 9% of patients underwent reoperation for recurrent symptoms
      failures occurred within 24 months of operation
    - Complications : ipsilateral deaf ear in 2.6%
      ipsilateral permanent, severe facial weakness in 0.9%
      one operative death (0.1%)
      two brainstem infarctions (0.3%)