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PRIMER CURSO INTERAMERICANO DE
ACTUALIZACIÓN EN NEUROLOGÍA

Advances in Diagnosis, Neurobiology, and Treatment of Neurological Disorders

University of Miami, March 20 and 21, 2017

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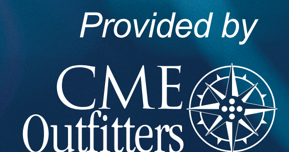

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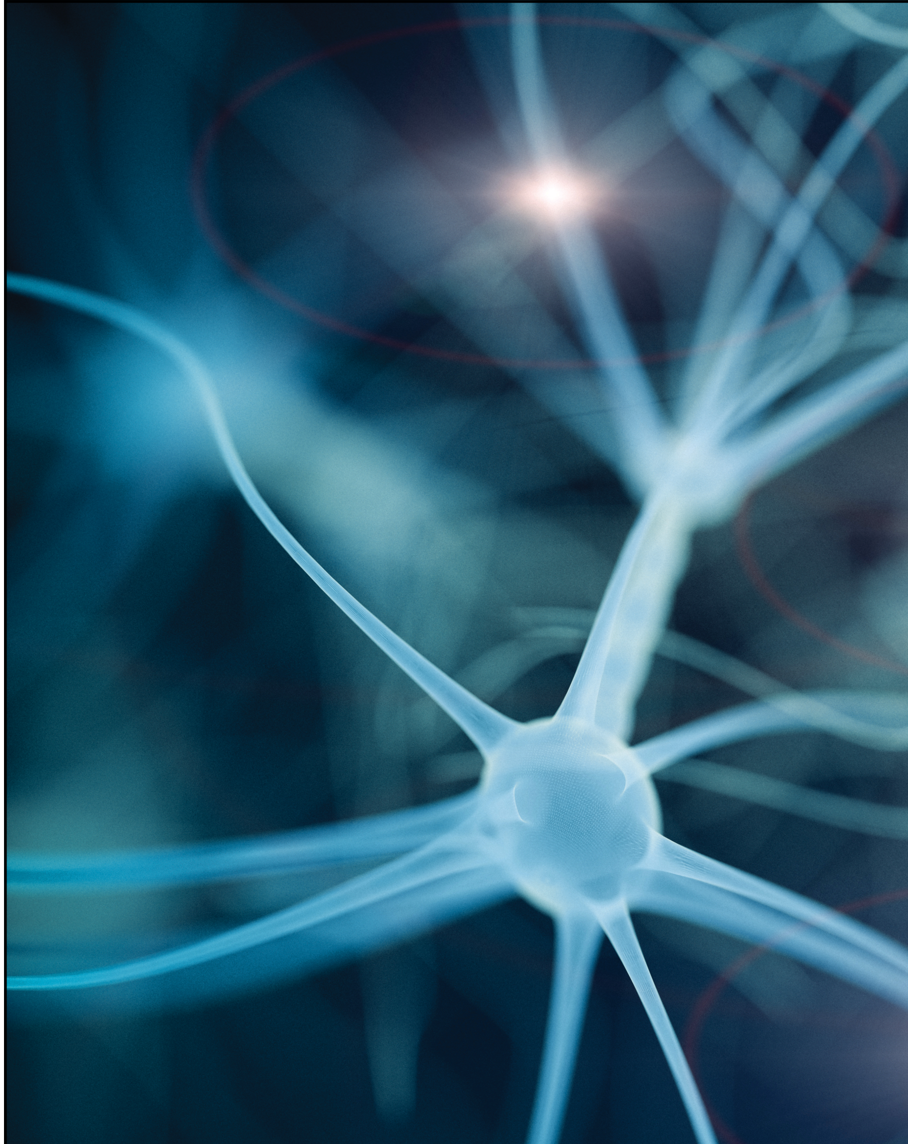
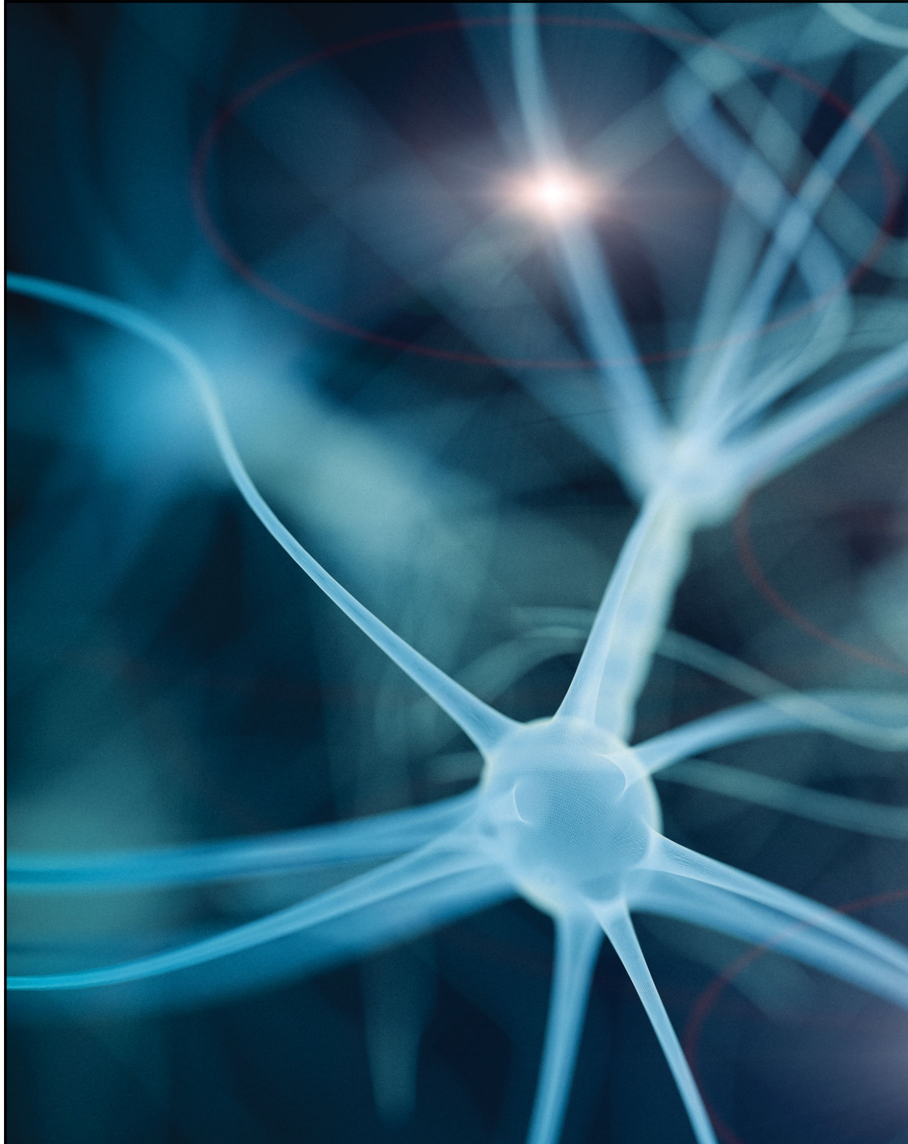
Mood Disorders in Common Neurological Conditions:

Partnering with Psychiatry to Improve Care of Patients



Learning Objective 1

Incorporate the treatment of comorbid mood disorders when developing a management plan for neurological conditions.



Learning Objective 2

Examine the neuroanatomical sequelae of mood disorders to facilitate treatment selection and management of patients with neurological conditions.

Mood Disorders in Neurologic Conditions

- Epilepsy
- Migraine
  - Bidirectionality unipolar bipolar
  - Acute triptans
  - Prophylactic anticonvulsants
  - Botoxulinlim toxin
- Stroke
  - Prelinical stroke models and mood stabilizers
- Parkinson's disease
  - Dopamine dysregulation syndrome
  - Deep brain stimulation (DBS)
- Multiple sclerosis
- Pseudobulbar affect

Evidence Base Limitations

- Patient cohort
  - Community, speciality clinic, hospital
- Symptoms vs. disorder (ie. structured diagnostic interview)
- Screening instrument for diagnosis (MDQ)
  - Screening instrument ≠ diagnosis
- Screening instrument for symptom burden (PHQ9, PHQ2)
  - Symptom confound
  - No established reliability validity in the neurologic diagnosis

Evidence Base Limitations

- Drug adverse events resemble disease
- Outcome measures
  - Different time of repsonse
  - Degree of repsonse
- Missed mood diagnoses and no / undertreatment

Migraine Epidemiology

- Migraine prevalence: 17% of women, 6% of men
- ↑ risk of psychiatric comorbidity in migraine and other headache disorders
  - Depression: 2-4x higher, bidirectional
  - Bipolar disorder: 3-7x higher (higher if aura)
- Higher levels of anxiety & depression in chronic migraine than episodic migraine

Lipton RB, et al. *Neurol*. 2007;68☹5)343-349. Hamelsky SW, et al. *Headache*. 2006;46(9)1327-1333.
Baskin SM, et al. *Headache*. 2006;46 Suppl 3:S76-87.

Basis of Comorbidity:
Migraine, Anxiety & Depression

- Genetic correlation: twins studies
  - Migraine more heritable when no depression
  - Bidirectional causality: one causes the other
  - Syndromic association: spectrum disorder
- Common biologic neurotransmitter substrate
  - Low serotonin levels
  - Abnormal tyrosine metabolism on DA/NE synth
- Imbalanced glutamatergic & GABAergic activity?

Casucci G, et al. *Neurol Sci.* 2010;31(Suppl 1:s99-101; Ligthart L, et al. *Headache*. 50(10):1549-1560.

Headache & Depression

- Dual-action antidepressants: 5-HT, NE reuptake
  - Amitriptyline, nortriptyline
    - 25-50mg/d for headache, 150 mg/d for depression
    - Sedation, urinary retention, weight gain, blurred vision
    - Overdose of 3-5 times daily dose can be fatal
  - Venlafaxine
    - 75-150mg/d for migraine, tension headache
  - Mirtazapine—complex action
    - Second line after amitriptyline for tension headache
- Beta blockers probably OK

Silberstein SD, et al. *Neurology*. 2000;55(6):754-762; Bulut S, et al. *Clin Neurol Neurosurg*. 2004;107(1):44-48; Ozyalcin SN, et al. *Headache*. 2005;45(2):144-52; Bendtsen et al. *Neurol*. 2004;25;62(10):1706-1711; Ko DT, et al. *JAMA* 2002;288(3):351-357; Van Melle et al. *J Am Coll Cardiol*. 2006;48(11):2209-2214.

Headache & Bipolar Disorder

- Anticonvulsant mood stabilizers for migraine
  - Valproate (Level A)
  - Topiramate (A)
  - Carbamazepine: bipolar, possibly migraine (C)
- Not dual efficacy
  - Gabapentin: migraine, not bipolar
  - Lamotrigine: bipolar, not migraine (maybe aura)
- Avoid antidepressants for headache without mood stabilizer → precipitate mania

Silberstein SD, et al. *Neurology*. 2012;78(17):1337-1345.

Medication-Related Issues

- Anti-epileptics and suicide event risk
  - FDA 2008 meta-analysis: 1.8 fold increased risk among 11 AEDs in patients with epilepsy, pain, or psychiatric disorders
  - 0.24% in placebo to 0.43% in AED (1.9 more per 1000)
  - Subsequent studies: ↑ risk except in epilepsy
- Serotonin syndrome with triptans + SSRIs/SNRIs
  - FDA 2006 warning based on n = 10 (none met Hunter criteria).
  - AHS 2010: “insufficient class IV data to limit use; be vigilant”; 700,000 taking both in US

Arana A, et al. *N Engl J Med*. 2010;363(6):542-551; Evans RW, et al. *Headache*. 2010;50(6):1089-99.

Botulinum Toxin in Migraine & Depression

- Reversible acetylcholine (ACH) inhibitor and subsequent neuromuscular blocking agent
- OnabotululinumtoxinA (OBA) FDA approval:
  - Frown & crow's feet lines (cosmetic)
  - Blepharospasm
  - Cervical dystonia
  - Chronic & episodic migraine
    - 155 units, 0.1 ml (5 units) differentially distributed across 7 head/neck muscles q 12 weeks

Botulinum Toxin in Migraine & Depression

- 2 controlled (+) studies OBA in major depression
  - 6-week single injection OBA (29F/40M units) across 5 sites vs. saline injection (n=85)
  - 24-week cross-over study single injection of OBA 29F/39M
- Facial feedback hypothesis and emotional proprioception

Epilepsy & Mood Disorder Diagnosis

- Depression prevalence
  - 20-30% (community base)
  - 20-55% (specialty epilepsy clinic)
- Bipolar disorder
  - Both highly heritable, episodic course (kindling?)
  - 2X prevalent in self-reported epilepsy
  - Prodromal, postictal, AED adverse event
  - Disorder (12%) symptoms (15%)
    - temporal lobe epilepsy
- FDA and/or evidence base
  - Valproic acid, carbamazepine, lamotrigine: bipolar
  - Binge eating disorder, alcohol use disorder, gambling: topiramate

Epilepsy & Mood Disorder Treatments

- Antidepressants in non-epileptic patients
  - Pro-convulsant (maprotiline, clomipramine > 200 mg, amitriptyline > 200 mg, bupropion > 450 mg IR)
  - Sertraline, mirtazipine, paroxetine < expected rate
- Carbamazepine p450 hetero-induction
  - Mirtazipine, venlafaxine, bupropion
  - Antipsychotics (quetiapine, risperidone)
- Topiramate & zonisamide
  - May reverse atypical antipsychotic induced weight gain
- Osteoporosis associated with:
  - p450 inducing AEDs (CBZ, OXC) vs non-inducing (LTG, VAL, TPX)
  - SSRI's
  - Depression, epilepsy, and peri / post menopause SSRI

Post Stroke Depression (PSD)

- American Heart Association 2015
  - 700,000 strokes annually, 163,000 stoke related deaths
  - 85% ischemic, 12% hemorrhagic
- 31% of post stroke patients (n=25,488) developed depression up to 5 years follow-up
- Meta-analyses demonstrate antidepressant efficacy & prevention of PSD
  - SSRI risks- hemorrhagic complications, GI bleeding, falls

Robinson RG, Jorge RE. *Am J Psychiatry* 2016;17(3):221-231.; Santos et al. *Cerebrovas Disease* 2011, Coupland C, et al. *BMJ* 2011;343:d4656.; Hackett et al., Cochrane Data Base 2008

Post Stroke Depression (PSD)

- Post stroke anatomy
  - Mania: right sided lesions, (+) vascular risk factors
  - Depression: distance from anterior border of lesion from left frontal pole cortical & subcortical (? 2 months)

Robinson RG, Jorge RE. *Am J Psychiatry* 2016;17(3):221-231.; Santos et al. *Cerebrovas Disease* 2011, Coupland C, et al. *BMJ* 2011;343:d4656.; Hackett et al., Cochrane Data Base 2008

Mood Stabilizers in Preclinical Stroke Models (Li, DVPX, LTG)

- Neuroprotective (improved neurological deficit, reduced brain infarct volume) in focal & global cerebral ischemic models

- Lithium via glycogen synthetase kinase 3 (GSK-3)
- Lamotrigine via voltage gated sodium channels (VGSCs)Valproic acid - Histone deacetylases (HDACs) inhibition
  - transcriptional production of neuroprotective & neurotrophic (BDNF) gene products

Wang et al., Acta Pharmacologica 2011, Leng et al., 2012, Croarkin et al., 2014

Parkinson's Disease & Depression

- Spectrum of Depression
  - Depressive symptoms (50-70%)
  - Clinically significant symptoms (35%)
  - Major depressive disorder (17%)
  - "Off" only (%?)
- Meta-analysis (n = 13 studies)
  - Both SSRI's aggregate & CBT > placebo
- Bupropion improves depression & motor symptoms
- Pramipexole controlled evidence
  - Depressive symptoms + PD
  - Major depressive disorder
  - Bipolar I/II depression

Corrigan et al., Dep/Anxiety 2000, Bomasang-Layno et al., Parkinson Rel Dis 2015, Goetz et al., Neurology 1989, Cooney & Stacy Curr NBurol 2016, Goldberg et al , Am J Psych 2004, Zarate etl., Biol Psy 2004

Parkinson's Disease Psychosis (PDP)

- Psychosis in PD > 50% patients, >75% PD dementia
- Clozapine & Parkinson Study Group
  - 14 months clozapine (mean dose 25 mg) improved psychosis with no exacerbation in UPDRS score
  - Weaker D2 affinity / greater affinity for D4, 5HT2A, D1
- Quetiapine controlled investigations
  - 1 (+) and 3(-) studies depressive symptoms (50-70%)

Cooney & Stacy Curr Neurol 2016, PSD NEJM 1999; Fernandez et al., 2009; Ondo et al., 2005, Rabey et al., 2007, Cummings et al., Lancet 2014

Parkinson's Disease Psychosis (PDP)

- Atypicals generally not effective / worsen motor symptoms
  - Limited evidence ziprasidone, olanzapine, aripiprazole
  - Risperidone worsens motor symptoms (D2 receptor affinity)
- Pimavanserin
  - "Atypical antipsychotic" FDA approved for PDP hallucinations/delusions
  - Inverse agonist and antagonist at 5HT2A and lesser extent 5HT2C

Cooney & Stacy Curr Neurol 2016, PSD NEJM 1999; Fernandez et al., 2009; Ondo et al., 2005, Rabey et al., 2007, Cummings et al., Lancet 2014

FDA Approval Status for DBS Neuromodulation

- Full FDA approval
  - DBS Essential tremor-1997
  - DBS Refractory Parkinson's Disease-1997
  - RNS Refractory partial epilepsy-2013
    - Responsive NeuroStimulation (RNS)
  - DBS Treatment Resistant Epilepsy
    - FDA review of SANTE 5-year data (Sz reduction 41% 1yr, 69% 5yr)
- Humanitarian Device Exemption (HED)* approval
  - Dystonia (2003)
  - Obsessive compulsive disorder (2009)

*1. intended for fewer than 4,000 people in the US every year, 2. demonstrate the product's safety and probable benefit, 3. IRB approval required each center

STN-DBS and Suicide

- International multicenter retrospective survey followed by case-control study (n = 5311)
- Results
  - Completed Suicide: 0.45% (24/5311)
  - Attempted suicide: 0.90% (48/5311)
  - 75% events occurred within 17 months postoperatively
  - Suicide rate significantly higher than country specific rate
- Risk Factors ($P < .05$)
  - Single
  - Younger age (52.9$\pm$3.5 yrs)
  - Early PD onset
  - Postoperative depression
  - Previous suicide attempt
  - History of impulse control D/O
  - Compulsive medication use
- Suicide attempts not associated with motor outcomes

Voon V, et al. *Brain*. 2008;131(Pt 10):2720-2728.

Underlying Neurobiology and Clinical Correlates of STN DBS-Induced Mania (N = 17)

- Ventromedial electrode placement 14/17 (82%)
- Reproducible mania with ventral stimulation
  - Anterior cingulate & medial prefrontal cortex activation
- Mania resolved switch to dorsolateral placement 12/14 (86%)
- Additional coorelates: Unipolar stimulation, higher voltage (3 V), male sex, and early-onset PD.
- Preclinical model voltage increase (3V to 7V) associated with progressive increase in striatal dopamine release

Chopra A, et al. *J Neuropsychiatry Clin Neurosci*. 2012;24(1):102-110.

DBS Target For Depression: Rationale for Subcallosal Cingulate Gyrus

- Subcallosal Cingulate Gyrus White Matter (SCG wm)
- BA25 is metabolically overactive in TRD
  - Positive correlation with depressive symptom severity
- BA25 activation at baseline is normalized by treatment:
  - Sertraline
  - Venlafaxine
  - Fluoxetine
  - ECT
  - rTMS
  - Placebo
  - Responder vs. non-responder

Mayberg HS, et al. *Br Med Bull*. 2003;65:193-207; Kennedy SH. *Ann Clin Psychiatry*. 2007;19(4):279-287; Drevets WC, et al. *Pharmacol Biochem Behav*. 2002;71(3):431-447; Mottaghy FM, et al. *Psychiatry Res*. 2002;115(1-2):1-14.

Subcallosal Cingulate DBS for Treatment Resistant Unipolar or Bipolar Depression

- Rigorous study design
- Single blind sham stimulation phase
- 24 week open label active stimulation
- Single blind discontinuation
- 2-year follow up
- N = 17 (10F) – 300 screened
- Mean duration index episode 65 months, 6.2 AD Rxs
- Response/Remission 41%/18% 24 wks, 92% / 58% 2 yrs
- Discontinuation recurrence 3/3 (100%)
- UP = BP

Holtzheimer PE, et al. *Arch Gen Psychiatry*. 2012;69(2):150-158.

DBS Target For Depression: Rationale for Ventral Capsule/Ventral Striatum* (VC/VS)

- Ventral Capsule/Ventral Striatum (VC/VS)*
- Mood elevation in patients with OCD during DBS and benefit of mood improvement in MDD/OCD
- Proximity to NAc & stimulation of reward circuitry
- Marker of hedonic tone in depression
- Neighboring targets:
  - Anterior Limb of Internal Capsule (ALIC)
  - Nucleus Accumbens (NAc)

Greenberg BD, et al. *Neurosurg Clin N Am*. 2003;14(2):199-212; Abelson JL, et al. *Biol Psychiatry*. 2005;57(5):510-516; Heien ML, et al. *CNS Neurol Disord Drug Targets*. 2006;5(1):99-108.

DBS Targets for Depression

- Initial encouraging results for Subgenual cingulate and VC/VS, but negative or failed RCTs
- Need to address study design
  - Neurosurgery variability
  - Stimulation parameters based on Parkinson's
  - Bipolar stimulation parameters (unipolar better ?)
  - Time points of assessment and trial duration
  - TRD diagnostic heterogeneity
- Enthusiasm for medial forebrain bundle & lateral habenula
- All future DBS TRD studies will require preclinical research to guide clinical trial development
  - Targets SGC, VCVS, NAc, MFB, LHb
  - White matter circuitry –multiple entry points to network

Multiple Sclerosis & Depression

- 25–50% of MS patients develop major depression
  - 2-5X higher than general population
  - Relapsing-remitting MS > progressive MS
  - CNS inflammation, ↓neurotrophic characteristic of both
- Atrophy and lesion volume
  - T2-hype & T1-hypointense lesions dominant medial inferior frontal
  - More-extensive atrophy in dominant anterior temporal areas
- Treatment interventions
  - Desipramine marginally effective poorly tolerated
  - Paroxetine dose escalation based on symptom response
    - Response (50% ↓HRSD) = 57% vs. PLC= 40%
    - Completer analysis 78% vs 42% - neither $p < .05$
  - Sertraline & cognitive-behavioral therapy (CBT) > supportive-expressive group therapy (SEG)
    - by Beck Depression Inventory BDI-18 (eliminates 3 MS confounds), but not Hamilton Rating Scale for Depression

Pioro et al. *Drugs*. 2011;71(9):1193-1207; Ahmed A, et al. *Ther Clin Risk Manag*. 2013;9:483-489.

Multiple Sclerosis & Bipolar Disorder

- Bipolar disorder in MS: at initial DX (3.15%) & overall (4.2%)
- MS Case (n = 201) vs control (n = 804) DSM-IV interview
  - ↑ prevalence: BD I ($p=0.05$) BD II ($p<0.0001$) cyclothymia ($p=0.0001$)
  - MDD / cyclothymia lower among cases ($p<0.005$)
- Autoimmune association ?
  - MS + psychotic manic episode associated with 3 new T2 lesions - rapidly response IV methylprednisolone + risperidone
  - MS + manic episodes more likely in patients with higher brain lesions
- DSM5 implications corticosteroid-or AD Rx -induced mania
- Steroid mania response to mood stabilizers (Li, RIS, OLZ)

Hotier et al., *Gen Hosp Psychiatry* 2015, Ron et al., Psychol Med 1989; Carta et al , JAD 2014, Marrie et al., Neurology 2016

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Pseudobulbar Affect

- Uncontrolled crying and/or laughing disproportionate or inappropriate to social context
- US online study (PD, TBI, ALS, MS, CVA, AZ) prevalence
  - 9.4-37.5% (1.8-7.1 million)
  - 30-35% comorbidity with depression
- Center for Neurologic Study – Lability Scale (CNS-LS)
  - 7 item self rated questionnaire validated in MS and ALS
  - ≥13 predicted 82% clinical diagnoses of MS
- Disruption of corticopontine – cerebellar circuits impairing cerbebellar modulation “gate control”
- 6 studies SSRI/TCA = dextromethorphan/quinidine > placebo
- Dextromethorphan 20 mg/quinidine 10 mg (1-2 caps qd)
  - Quinidine blocks 1st pass hepatic metabolism
  - No cardiac effects

Pioro EP, et al. *Drugs*. 2011;71(9):1193-1207.; Ahmed A, et al. *Ther Clin Risk Manag*. 2013;9:483-489.

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Questions & Answers

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