Spectrum of Disinhibition Syndromes post-TBI….from PBA to Shopping

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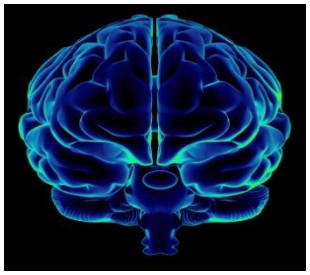
Disclosure

- I have been a paid consultant to Avanir Pharmaceuticals; also on their Speaker's Bureau
- I have stock in Avanir
- Avanir is not compensating me for tonight's lecture, nor are they paying for any conference-related expenses.

Outline

- Disinhibition/Impulsivity
- PBA
- Agitation/anger/irritability
- Suicidal Ideation
- Compulsive shopping
- Treatment with DM/Q
- Case Studies

Disinhibition and Impulsivity after Traumatic Brain Injury (TBI)



- Inhibitory control is the ability to suppress irrelevant or interfering stimuli
- Deficits of impulse control are characterized by an unrestrained desire to fulfill sudden urges
- Impulsiveness can occur within any or all domains of functioning (emotional, behavioral, and cognitive)
- Prevalence estimates of these disorders after TBI range from 5%–70%[1]
- Damage to the orbital-frontal regions typically cause disinhibition, while injury to the dorsal-medial regions cause impulsivity[2]

[1]Silver JM, Yudofsky SC. *Neuropsychiatry of Traumatic Brain Injury.* Washington DC: American Psychiatric Press; 1994.
[2]Duffy JD, Campbell JJ. The regional prefrontal syndromes: A theoretical and clinical overview. *J Neuropsychiatry Clin Neurosci.* 1994;6:379–387.

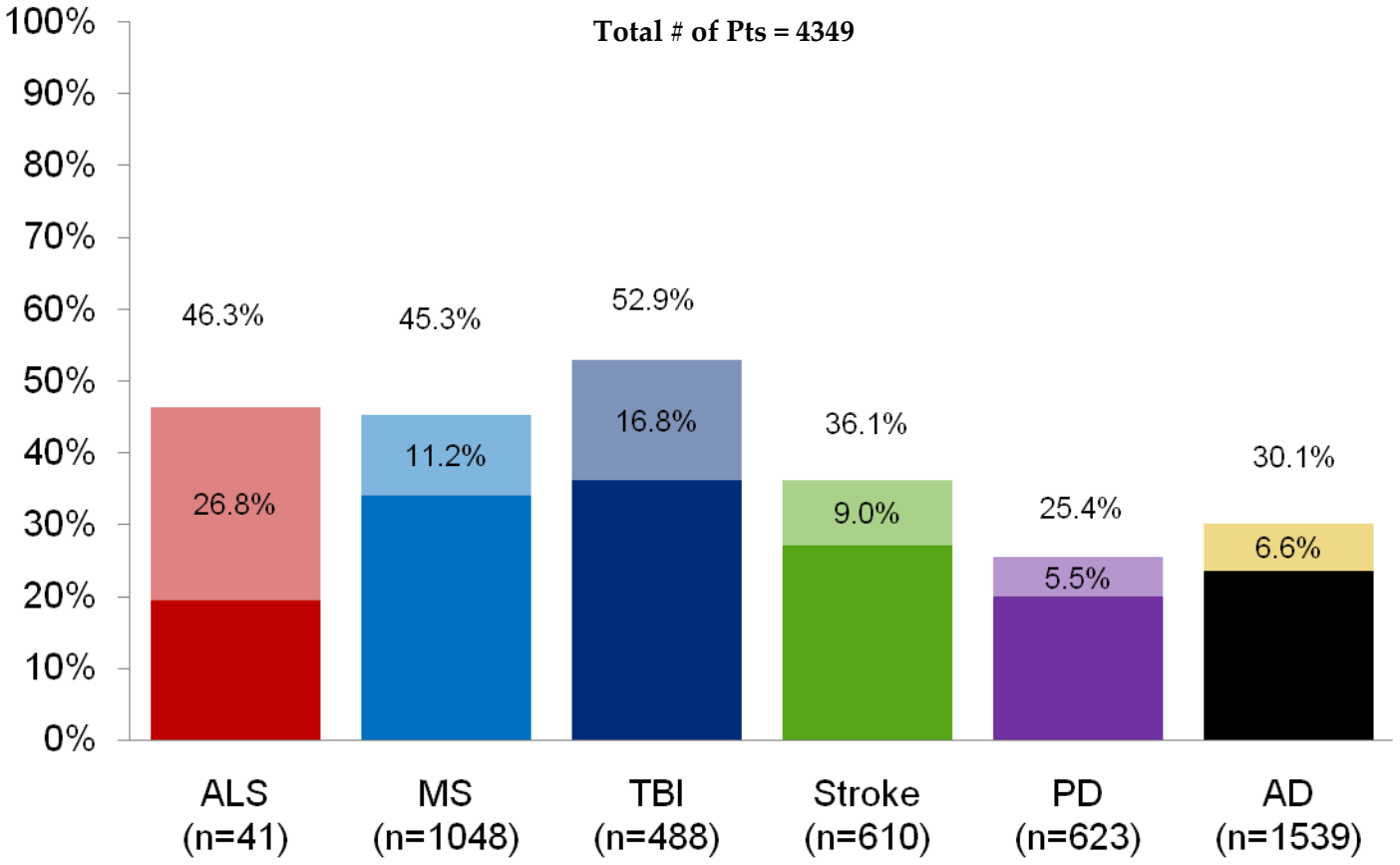
Pseudobublar Affect (PBA)….Affective Incontinence

- Can occur secondary to various neurological disorders (Alzheimer's, ALS, MS, Parkinson's, Stroke, TBI)[1]
- Prevalence estimates of PBA associated with TBI have been under reported, and actually exceed more than 55% of survivors[1,2]
- Differentiated from primary mood and anxiety disorders since PBA is comprised of transient paroxsyms of affect that are either contextually inappropriate, incongruent or exaggerated relative to underlying mood states[3]
- Can be associated with significant psychosocial disability, including withdrawal and social isolation[4]

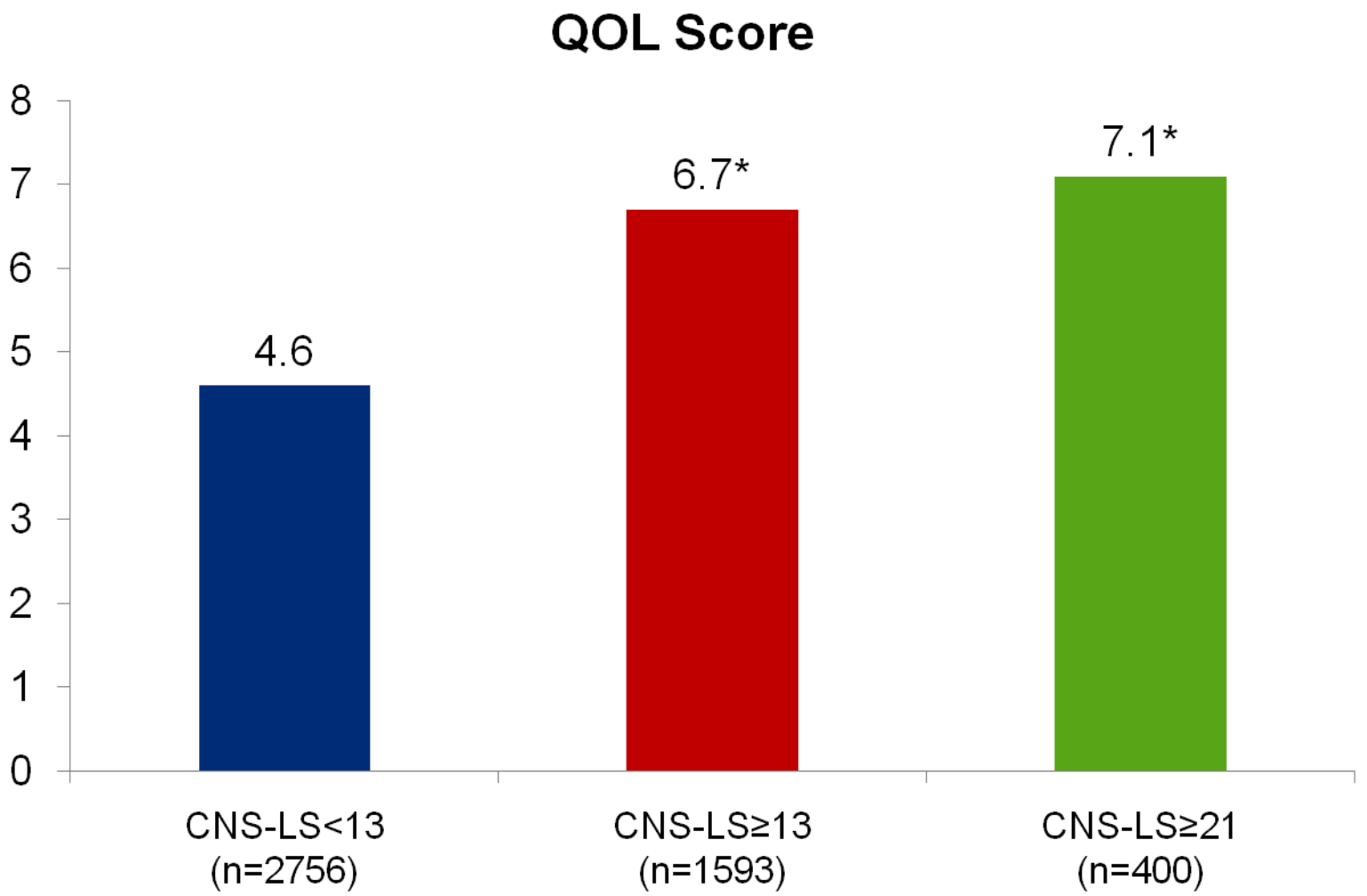
- [1]Tateno A, Jorge RE, Robinson RG. Pathological laughing and crying following traumatic brain injury. *J Neuropsychiatry Clin Neurosci.* 2004;16:426-434.
- [2]Fellus JL, Kantor D, Kaye RE. PRISM registry: A novel research tool to determine the prevalence of pseudobulbar affect. *Eur Neurol.* 2012;19: 85.
- [3]Parvizi J, Coburn KL, Shillcutt SD, et al. Neuroanatomy of pathological laughing and crying: A report of the American Neuropsychiatric Association committee on research. *J Neuropsychiatry Clin Neurosci..* 2009;21:75-87.
- [4]Dark FL, McGrath JJ, Ron MA. Pathological laughter and crying. *Aust N Z J Psychiatry.* 1996;30:472-479.

Estimated PBA Prevalence by CNS-LS Threshold
Interim PRISM Data - June 30, 2012

Current Percentage of Patients with CNS-LS score ≥ 13 = 36.6%
Current Percentage of Patients with CNS-LS score ≥ 21 = 9.2%



Impact of Neurological Condition on Quality of Life by CNS-LS Threshold Interim PRISM Data - June 30, 2012

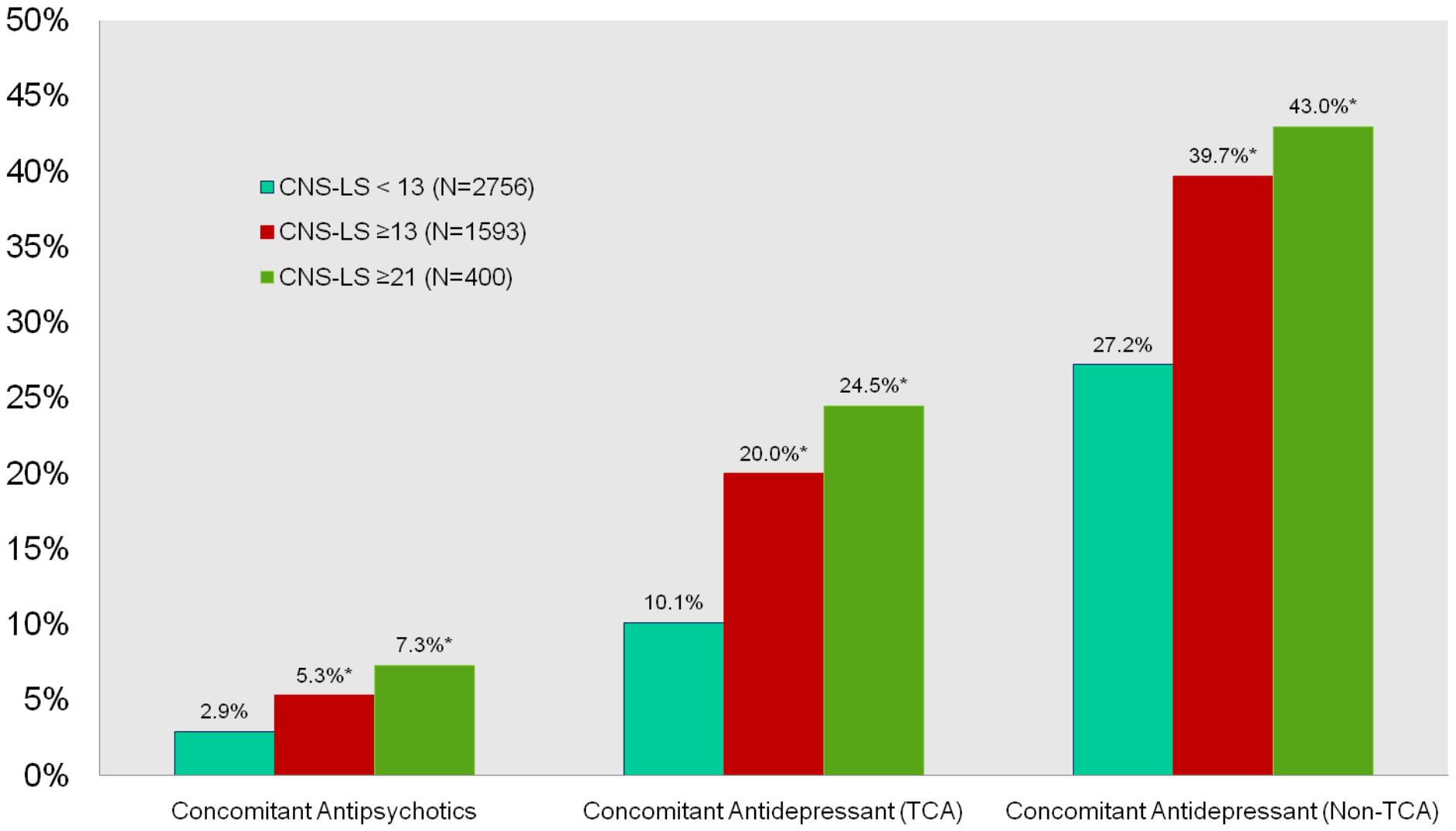


Quality of Life (QOL) Scale

How has your neurologic condition affected your quality of life? Indicate by selecting a number on the scale below:

(Not at all) 0-----1-----2-----3-----4-----5-----6-----7-----8-----9-----10 (Strongly Affected)

Psychotropic Medication Use By CNS-LS Threshold
Interim PRISM Data – June 30, 2012



Agitation/Anger/Irritability

- Also common post TBI 30-70%
- Often associated with frontal damage (release) but also related to overall confusion (PTA)
- Can be secondary to other meds (including paradoxical reaction)
- Typically treated with aggressive, often polypharmacologic regimes
- Disrupts/wastes time in rehab therapy sessions
- Distressing to caregivers
- “inappropriate” “excessive” used in literature

Recent Treatment of Irritability

- “Thus, amantadine appears to be a beneficial treatment for reducing the frequency and severity of irritability that accompanies chronic TBI.”
- Amantadine known to have NMDA modulation activity (in addition to obvious DA action)
- Some studies note memantine (Namenda) helps the agitation in Alz. Dz

Suicidal Ideation (SI)

- Depression is common post TBI
- SI is common
- Dysexecutive function and cognitive inflexibility significantly raise the risk of attempted/completed suicide
- Disinhibition therefore plays a major role in the translation of depressive thought into the act of suicide attempts
- Recently high profile athletes and military with TBI/CTE-associated suicidality

Recent Experience with SI post TBI

In a recently submitted paper describing a cohort of 6 individuals with acquired brain injury (TBI n=5), treatment of PBA was associated with several unexpected salubrious benefits, in addition to ameliorating PBA:

- Rapidly abolished Suicidal ideation (SI)
  - Within 1-3 doses
- Alleviated chronic depression and irritability
- ….**despite** all pts. *already* being maintained on 1-4 mood elevating or stabilizing drugs

OCD behavior post-TBI

- OCD is common
- Perseveration overlap?
- Sometimes called Impulse Control Disorder (ICD)
  - Literature describes that “some feel CHI is a risk for developing ICD, such as excessive shopping”
- Again, complex interplay between cognition, mood and behavior (and underlying anatomic correlates, e.g. frontal, limbic circuits)

Compulsive (?impulsive) Shopping

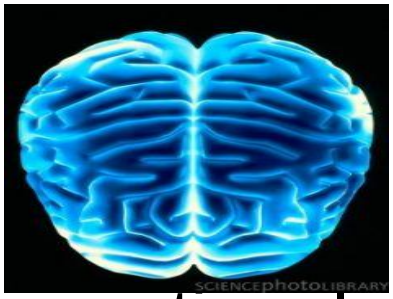
- Remarkably “hidden” except when extreme
  - “don’t ask don’t tell…”
- Study released in May 2012 described memantine treatment reduced compulsive shopping in (***non-TBI***) cohort.
- The NMDA mechanism lead me to query pts…
- Now 7 TBI pts. report compulsive or impulsive shopping
- In some cases, poor STM may play a role
  - ?perseverative buying (the same thing)

Treating PBA post-TBI with DMQ[1]

In a cohort of individuals with acquired brain injury, treatment with DMQ demonstrated several unexpected salubrious benefits, in addition to ameliorating PBA:

- Rapidly abolishing SI
- Alleviating chronic depression and irritability
- Diminishing aggressive behaviors and agitation
- Decreased frequency of compulsive shopping

[1]Fellus JL, Defina PA, Zakrzewski CM. Dextromethorphan/quinidine alleviates pseudobublar affect and rapidly eliminates suicidal ideation in individuals with acquired brain injury: A case-series. 2012; submitted to *CNS Spectrums*.



Treatment for PBA

- Conventional antidepressant pharmacotherapies that modulate serotonergic and noradrenergic neurotransmission were frequently used to treat PBA (SSRIs, SNRIs, TCAs)[1,2]
- Dextromethorphan/quinidine (DMQ, 20/10, Avanir Pharmaceuticals, Nuedexta) has recently been shown to robustly diminish the frequency and severity of PBA episodes arising from various neurological disorders[3,4]
- Dextromethorphan is a non-competitive antagonist of the NMDA receptor and σ-1 receptor agonist, thereby modifying monoaminergic and glutamatergic neurotransmission[5]

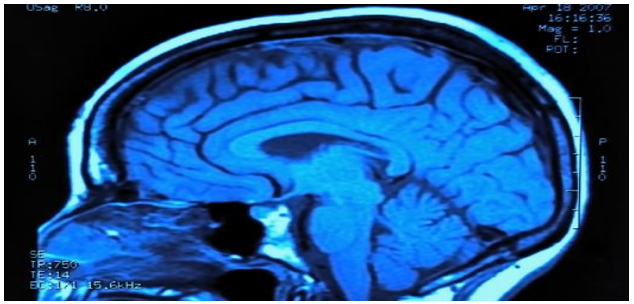
[1]Kim SW, Shin IS, Kim JM, et al. Mirtazapine treatment for pathological laughter and crying after stroke. *Clin Neuropharmacol.* 2005;28;249-251.

[2]Ferentinos P, Paparrigopoulos T, Rentzos M, et al. Duloxetine for pathological laughter and crying.*Int J Neuropsychopharmacol.* 2009;12:1429-1430.

[3]Rosen H. Dextromethorphan/quinidine sulfate (zeniva) for the treatment of pseudobulbar affect. *Drugs Today (Barc).* 2008;44:661-668.

[4]Schiffer R, Pope LE. Review of pseudobulbar affect including a novel and potential therapy. *J Neuropsychiatry Clin Neurosci.* 2005;17:447-454.

[5]Maurice T, Su TP. The pharmacology of sigma-1 receptors. *Pharamacol Ther.* 2009;124:195-206.



Case 1

32 y.o. female severe TBI at18 y.o., MVC

Stable history of PBA and chronic depressed mood since TBI

Paroxsymal episodes of rage and aggression created intense interpersonal conflicts and loss of employment, which triggered periods of deep depression dominated by acute suicidal ideation and uninhibited crying

Attempted treatment with a total of 7 SSRIs/SNRIs/mood stabilizers without therapeutic benefit over 13 years

Within a few hours of her first dose of DMQ, she reported a remarkable elevation in her mood, suicidal ideation completely resolved and PBA episodes remitted

Followed a naturalistic, retrospective ABAB design (lapsed insurance coverage forced her to repeatedly discontinue treatment) mood cycled from mildly euphoric to severely depressed with significant suicidal ideation within weeks

With each resumption of DMQ therapy, she report,s “within a few hours of taking Nuedexta, a sense of calm settles in and I know everything is going to be okay.”

Case Study 2 of PBA in TBI

- 42 y.o. personal trainer, TBI from MVC 13 yrs ago
- Referred to “follow with your neurologist” pre-op
- Still had crying, anger/irritability, back pain, compulsive shopping, poor/restless sleep; residual cognitive impairment (“cloudy”)
- Failed prior SSRI's, buspirone; VPA
- Screened positive for PBA, CNS-LS=22
- Rx DM/Q (Nuedexta; 20mg/10mg) for his PBA
- RTC 3 weeks later reporting:
  - Crying, anger, back pain **resolved**
  - Can “think more clearly"; Sleeps better
  - Dramatically less compulsive shopping: “now I got money in the bank!”

Nuedexta modulates NMDA activity which seems to lead to….

- Better impulse control (anger/agitation post stroke, TBI, anoxia)
  - Pts. Have told me DM/Q "lends pause", allowing more time to process before reacting (inappropriately/impulsively)
- Crying/laughing (some describe laughing while trying to be angry)
- Suicidal ideation
- Compulsive shopping
- Current testing for Alzheimers agitation; already seeing TBI clinical benefit
- Autism-related behaviors…some OCD-like
- _____
- Other reported improvements
  - Speech and swallowing in ALS
  - Central pain in MS
  - Chorea in Huntingtons

Summary

- Larger studies need to be done
- Broad activity of DM/Q….but full mechanism not currently understood.
- Very well tolerated
  - No patients in recent cohorts discontinued DM/Q
- Should be explored in military population given high rates of SI

- Thank you!
  - Questions?