COGNITIVE & BEHAVIORAL DISORDERS AFTER BRAIN INJURY: PHARMACOLOGIC TREATMENT OPTIONS

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AREAS COVERED

- PRINCIPLES
- MEDICATION USES BY DIAGNOSTIC CATEGORY
THE QUESTIONS
PRINCIPLES OF MEDICATION USE

- Withdraw offending meds when possible before starting new ones
- Individual responses vary enormously
- Medications can be combined—-with caution
  - Especially with different mechanisms of action
  - Check drug interactions
- “Start low, go slow”—when possible
- But don’t give up before going to high therapeutic doses…
  - If no side effects or contraindications
PHARMACOLOGY BY DIAGNOSIS (NOT JUST BY SYMPTOM)

- PRE-INJURY DISORDERS
- MEDICAL DISORDERS
- SLEEP DISORDERS
- SENSORY OR MOTOR DISORDERS
- MEDICATION-ADVERSE EFFECTS
- REACTIVE: DEPRESSION, ANXIETY
- ABI-PROVOKED PSYCHIATRIC DISORDERS: DEPRESSION, ANXIETY, PSYCHOSIS
- NEUROPSYCHOLOGICAL DISORDERS
PRINCIPLES OF DIFFERENTIAL DIAGNOSIS

- SYMPTOMS CAN FOOL YOU
  - E.G., “HALLUCINATIONS” MAY BE VISUAL-PERCEPTUAL + EXECUTIVE FX PROBLEM
  - E.G., REDUPLICATIVE PHENOMENON (CAPGRAS SYNDROME)
  - E.G., ABULIA/APATHY CAN BE A SYMPTOM OF DEPRESSION OR BE NEUROLOGICALLY BASED
  - E.G., AGGRESSION/AGITATION CAN BE PROVOKED BY UNDER-AROUSAL, POOR INITIATION, DEPRESSION
JUST POUR IT INTO MY FACE

I AM EXPERIENCING PRE-COFFEE AGITATION
PRINCIPLES OF DIFFERENTIAL DIAGNOSIS

- Ask Staff
- Ask Family
- Talk to the Patient!
NON-PHARMACOLOGIC TREATMENTS

- Optimize medical condition
- Treat sleep disorders
- Treat other disabilities
- Environmental modification
- Cognitive rehabilitation
- Individual counseling
- Motivational interviewing
- Group treatment
- S.A.D. lights
- Behavioral interventions
COMPLEX PARTIAL SEIZURES

- WITHDRAW OFFENDING AGENTS (E.G., TRICYCLIC ANTI DEPRESSANTS)
- ANTI CONVULSANTS
DEPRESSION

- WITHDRAW OFFENDING AGENTS (E.G., AMANTADINE, BACLOFEN)
DEPRESSION

- SSRI’s (E.G., (ES)CITALOPRAM, SERTRALINE, FLUOXETINE, FLUVOXAMINE, PAROXETINE*)
  - NEGATIVE TRIAL OF SERTRALINE IN TBI (ASHMAN ET AL, 2009)
  - SERTRALINE PREVENTED DEPRESSION IN ACUTE TBI, BUT ONLY WHILE GIVEN (NOVACK ET AL, 2009)
  - LOW/NON-SEDATING
  - LOW/NON-ANTI CHOLINERGIC (*EXCEPT PAROXETINE)
  - SIDE EFFECTS: NAUSEA, DIARRHEA, DECREASED LIBIDO, ERECTILE DYSFUNCTION, ANORGASMA, HEADACHE, DRY MOUTH, INSOMNIA, SEDATION, ANXIETY, SUICIDAL IDEATION, HEMORRHAGE (SEE BELOW), SMALL INCREASE ALL-CAUSE MORTALITY FOR >65 YEARS OLD
  - CITALOPRAM (& HENCE ESCITALOPRAM?) ASSOCIATED WITH SERIOUS CARDIAC ARRHYTHMIAS ABOVE 40 MG
  - INCREASED RISK OF GI & INTRACEREBRAL HEMORRHAGE, BUT CLINICAL SIGNIFICANCE IS LOW (HACCAM & MRKOBRA, 2012)
DEPRESSION

- **Vilazodone**
  - Inhibits serotonin (5-HT) reuptake
  - Partial agonist at 5-HT$$\text{$_{1A}$}$$ receptor

- **Vortioxetine**
  - Inhibits serotonin (5-HT) reuptake
  - Agonist at 5-HT$$\text{$_{1A}$}$$ receptors
  - Partial agonist at 5-HT$$\text{$_{1B}$}$$ receptors
  - Antagonist at 5-HT$$\text{$_3$}$$, 5-HT$$\text{$_{1D}$}$$, and 5-HT$$\text{$_7$}$$ receptors
DEPRESSION

- SNRI’s (E.G., VENLAFAXINE, DESVENLAFAXINE, DULOXETINE, MIRTAZEPINE, LEVOMILNACIPRAN)
  - LOW/NON-SEDATING*
  - LOW/NON-ANTICHOLINERGIC
  - SIDE EFFECTS: SIMILAR TO SSRI’S
    - BUT CAN RAISE BP
    - *MIRTAZEPINE IS GENERALLY SEDATING & OFTEN CAUSES WEIGHT GAIN
DEPRESSION

- VILAZODONE-COMBINED SSRI & SEROTONIN 1A RECEPTOR PARTIAL AGONIST
- BUPROPION-NORADRENALINE & DOPAMINE REUPTAKE BLOCKER
  - AVOID OR USE CAUTIOUSLY (SEIZURES AT HIGH DOSES?)
  - 1-YR SZ RATE AT MAX 300 MG/DAY IN NON ABI, NON-EPILEPTIC, NON-EATING DISORDER POPULATION = 0.15% (DUNNER ET AL, 1998)
  - RISK IN SMOKING CESSATION SOME W/H/O SZ = 0.05% (N=168,000) (BEVINS ET AL, 2008)
  - LESS LIKELY TO CAUSE SEXUAL SIDE EFFECTS
- METHYLPHENIDATE? (LEE ET AL, 2005)
- METHYLPHENIDATE PLUS L-DOPA IMPROVE MOOD IN STROKE (DELBARI ET AL, 2011)
- IF INSOMNIA, SEDATING DRUG MAY HELP [E.G., MIRTAZEPINE, SEDATING TRICYCLICS, TRAZODONE-(NOT A GREAT ANTIDEPRESSANT)] (LARSON & ZOLLMAN, 2010)
DEPRESSION

- INCREASE DOSE AS INDICATED BEFORE GIVING UP
INSOMNIA

- TRAZODONE
- MELATONIN
- OTHER (NOT AS GOOD) ALTERNATIVES
  - OTHER SEDATING ANTIDEPRESSANTS
    - MIRTAZEPINE (REMERON): HALF-LIFE 20-40 HRS; WEIGHT GAIN
    - TRICYCLICS (DOXEPIN, AMITRIPTYLINE, NORTRIPTYLINE): LONG 1/2-LIVES, ACH EFFECT
      (LARSON & ZOLLMAN, 2010)
INSOMNIA

- BENZODIAZEPINES
  - LORAZEPAM-COGNITIVE SIDE EFFECTS IN AM (DAWSON ET AL, 2008)
  - OXAZEPAM-NO COGNITIVE SIDE EFFECTS IN AM (FELDMEIR ET AL, 1983)

- OTHER GABA AGONISTS
  - ZOLPIDEM (AMBIEN)-AFTER 10 MG: COGNITION, DRIVING IMPAIRED IN AM (LEUFKENS ET AL, 2009); INTERFERE WITH NEUROPLASTICITY?
  - ESZOPICLEONE [LUNESTA])
    - CONFLICTING EVIDENCE ON COGNITIVE, DRIVING IMPAIRMENT IN AM (BOYLE ET AL, 2008; FDA, 2014)
    - FDA CHANGED STARTING DOSE TO 1 MG DUE TO IMPAIRMENT (FDA, 2014)
    - INTERFERE WITH NEUROPLASTICITY?
  - ZALEPLON (SONATA): NO AM COGNITIVE EFFECTS WHEN GIVEN IN EVENING, BUT YES IF GIVEN IN THE NIGHT (LARSON & ZOLLMAN, 2010)
If they had had Prozac
in the nineteenth century

Sure! Capitalism can work out its kinks!

Karl Marx
Hello, birdie!

Edgar A. Poe

Huguetta Mardel
ANXIETY

- BENZODI AZEPINES
- BUSPIRONE
- ANTI DEPRESSANTS (ESPECIALLY SSRI’s, SNRI’s)
- TREAT INSOMNIA
AROUSAL, INITIATION, PROCESSING SPEED, & ATTENTIONAL DISORDERS

- WITHDRAW OFFENDING AGENTS IF APPROPRIATE
  - ANTI CONVULSANTS
    - WORST OFFENDERS: PHENYTOIN, PHENOBARBITAL, TOPIRAMATE
    - NOT AS BAD: CARBAMAZEPINE, VALPROIC ACID
    - SEDATING, BUT NOT OTHERWISE COGNITIVE-IMPAIRED: GABAPENTIN
    - LEVITIRACETAM: STUDIES INDICATE LESS COGNITIVE-IMPAIRING, BUT ANECDOTALLY, MAY BE, ESPECIALLY RE: CONFUSIONAL STATE
  - NEUROLEPTICS/TYPICAL ANTI PSYCHOTICS (E.G., CHLORPROMAZINE, HALOPERIDOL, ETC.)
  - ATYPICAL ANTI PSYCHOTICS (E.G., QUETIAPINE, OLANZEPINE)
AROUSAL, INITIATION, PROCESSING SPEED, & ATTENTIONAL DISORDERS

- WITHDRAW OFFENDING AGENTS IF APPROPRIATE
  - BENZODIAZEPINES (E.G., DIAZEPAM, LORAZEPAM, CLONAZEPAM)
  - OTHER HYPNOTICS: DIPHENHYDRAMINE (BENEDRYL), OTHERS
  - ANTICHOLINERGIC DRUGS-CHRONIC USE ASSOCIATED WITH DEMENTIA
    - SEDATNG ANTIHISTAMINES: DIPHENHYDRAMINE, CHLORPHENIRAMINE
    - TRICYCLIC ANTIDEPRESSANTS: DOXEPIN, AMITRIPTYLINE
    - OVERACTIVE BLADDER INHIBITORS: OXYBUTYNIN (DITROPAN), TOLTERODINE (DETROL), TROPIUM (SANCTURA), OTHERS
  - ANTISPASTICITY AGENTS (BENZODIAZEPINES, BACLOFEN, TIZANI DI NE)
OTHER OFF-LABEL USES
AROUSAL, INITIATION, PROCESSING SPEED & ATTENTIONAL DISORDERS (& MEMORY?)

- CNS STIMULANTS AND DOPAMINERGICS
- STIMULATING ANTIDEPRESSANT: PROTRIPTYLINE
- MOST CAN CAUSE IRRITABILITY, ANXIETY, & PSYCHOTIC BEHAVIORS
- INVERTED U-SHAPED CURVE OF EFFECT-ESPECIALLY NMDA-RECEPTOR ANTAGONISTS
EFFECT vs DOSE

(Wood et al, 2014)
Alertness, Initiation, Attention, Speed

- Dopaminergic & Noradrenergic
  - Methylphenidate
    - Processing speed after TBI
    - Attention to task after TBI
    (Whyte et al., 2004; Wilmot & Ponsford, 2010—both RTC’s)
    - Motor function when combined with PT in stroke (Lokk et al., 2011)
  - Side effects: jitters/irritability, anxiety, depression, anorexia, psychosis, arrhythmias

- Dextroamphetamine (Focalin)
DOPAMINERGIC & NORADRENERGIC: AMPHETAMINES

NO GOOD STUDIES ON AMPHETAMINES IN TBI (FORSYTH R, COCHRANE DTBS REVIEW, 2006) EXCEPT LISDEXAMFETAMINE NE

- LISDEXAMFETAMINE NE
  - PRODRUG-CONVERTED TO DEXTROAMPHETAMINE NE
  - BYPASSES 1ST PASS METABOLISM (MECHANISM UNKNOWN) & SO SLOWS CONVERSION
  - DECREASES “LIKING” EFFECT (DOMNITEI & MADAAN, 2010)
  - RCT IN PTS WITH TBI: SHOWS BENEFIT FOR SUSTAINED ATTENTION, WORKING MEMORY, RESPONSE SPEED STABILITY AND ENDURANCE, AND SOME EXECUTIVE SKILLS (TRAMONTANA ET AL, 2014)
  - RCT IN MS PTS: IMPROVED PROCESSING SPEED & MEMORY; TREND FOR WM (MORROW ET AL, 2012)
  - SIDE EFFECTS: SAME
 ALERTNESS, INITIATION, ATTENTION, SPEED

- MIXED RESULTS OF AMPHETAMINES FOR MOTOR RECOVERY AFTER STROKE
  - DEXTROAMPHETAMINE
    - SIDE EFFECTS: JITTERS, ANXIETY, DEPRESSION, DECREASED APPETITE, PSYCHOSIS, ARRHYTHMIAS, HTN
  - AMPHETAMINE MIX (ADDERALL)
    - SIDE EFFECTS: SAME
ALERTNESS, INITIATION, ATTENTION, SPEED

- DOPAMINERGIC
  - MODAFINIL (PROVIGIL): SMALL RCT SHOWS BENEFICIAL EFFECT ON DAYTIME SLEEPINESS AFTER TBI (Kaiser, 2010)
    - NON-TBI STUDIES SHOW IMPROVED ATTENTION TOO (E.G., PILOTS)
    - LESS FREQUENT, BUT CAN CAUSE ANXIETY & PSYCHOTIC BEHAVIOR
  - ARMODAFINIL (NUVIGIL)
    - R-ENANTIOMER OF MODAFINIL
  - BROMOCRIPTINE (SEE ALSO “MEMORY” & “EXECUTIVE FX”)
    - NO OR WORSE ATTENTION IN TBI (Whyte et al, 2008)
    - ALERTNESS/ACTIVATION (MANY CASE REPORTS IN VS/MCS)
ALERTNESS, INITIATION, ATTENTION, SPEED

- NMDA RECEPTOR ANTAGONISTS
  - AMANTADINE (ALSO DOPAMINERGIC & NORADRENERGIC) (Sommerauer, 2011; Deep et al, 1999)
    - PILOT STUDY: TREND IN INPTS (Meythaler, 2002)
    - RCT-SPEEDS RECOVERY IN MCS PATIENTS (Giacino et al, 2012)
    - RCT-DECREASES FATIGUE IN MS (Krupp et al, 1995)
  - SIDE EFFECTS: NAUSEA, ORTHOSTATIC DIZZINESS, EDEMA, LIVEDO RETICULARIS, DEPRESSION, ANXIETY/JITTERS, PSYCHOSIS, ARRHYTHMIAS, CONSTIPATION
ALERTNESS, INITIATION, ATTENTION, SPEED

- NMDA RECEPTOR ANTAGONISTS
  - MEMANTINE (NAMENDA)
    - INCREASED PREFRONTAL GLUCOSE METABOLISM ON PET SCAN CORRELATED WITH IMPROVED MMSE IN TBI
      - ALSO WERE AREAS OF DECREASED GLUCOSE METABOLISM
        (KIM, 2010)
    - SIDE EFFECTS: DIZZINESS, CONFUSION, CONSTIPATION, HTN, PSYCHOSIS, SOMNOLENCE, NAUSEA
ALERTNESS, INITIATION, ATTENTION

- NORADRENERGIC
  - ATOMOXETINE (norepinephrine transporter inhibitor)
    - RCT shows no effect on attention in TBI (Ripley et al., 2014)
    - Side effects: nausea, vomiting, hepatotoxicity, hypertension
  - PROTRIPTYLINE (neri tricyclic antidepressant)
    - Case series shows positive effects in ABI (Wroblewski et al., 1993)
    - Anticholinergic, lowers SZ threshold, 60-200 HR half-life
ALERTNESS, INITIATION, ATTENTION, SPEED

- ACETYLCHOLINESTERASE INHIBITORS (E.G., DONEPEZIL, RIVASTIGMINE, GALANTAMINE)
  - STUDIES SHOW POSSIBLE BENEFITS ON ATTENTION, WORKING MEMORY (IMMEDIATE MEMORY), SPEED OF PROCESSING AFTER TBI
  - ONE WAS LARGELY NEGATIVE

(SILVER ET AL, NEUROLOGY, 2006; ZHANG ET AL, ARCH PM&R, 2004)
ALERTNESS, INITIATION, ATTENTION

OCCASIONAL DRAMATIC RECOVERY IN DOC PATIENTS

- ZOLPIDEM (AMBIEN) (Claus & Nel, 2006; Whyte et al, 2008)
- BENZODIAZEPINES-EFFECT USUALLY NOT SUSTAINED WITH SUSTAINED TREATMENT (Glenn: Personal Communication)
MEMORY

- WITHDRAW OFFENDING AGENTS: ANTI CHOLINERGICS
- L-DOPA/CARBIDOPA
  - “MOTOR” (PROCEDURAL) MEMORY-HEALTHY YOUNG & ELDERLY (FLOEL ET AL, 2005A; FLOEL ET AL, 2005B)
  - EFFORTFUL EPI SODIC MEMORY- SMALL RCT, HEALTHY S’S (NEWMAN ET AL, 1984)
  - IMPROVED MOTOR FUNCTION ON RIVERMEAD MOTOR ASSESSMENT IN STROKE (SHEIDTMANN ET AL, 2001)
  - ADL’S & STROKE SEVERITY IMPROVE WHEN COMBINED WITH PT (LOKK, 2011)
- BROMOCRIPTINE
  - SPATIAL MEMORY-(LUCIANA ET AL, 1998)
- “NOOTROPS” (MALYKH, 2010)
  - PIRACETAM (CHOLINERGIC, OTHER MECHANISMS)
  - PRAMIRACETAM (CHOLINERGIC, OTHER MECHANISMS)
  - LEVITIRACETAM (VARI OUS MECHANISMS)
  - OTHERS
  - MAY HAVE POSITIVE EFFECT ON OTHER ASPECTS OF COGNITION TOO
EXECUTIVE FUNCTION

- BROMOCRIPTINE
  - STROOP, DUAL-TASK, FAS, TRAILMAKING, WCST (MCDOWELL ET AL, 1998)
  - WORKING MEMORY-NO (MCDOWELL ET AL, 1998)
  - WORKING MEMORY-YES (LUCIANA ET AL, 1992)
  - WORKING MEMORY 1 MONTH P-MTBI-NO (MCALLISTER ET AL, 2011)
NON-FLUENT (EXPRESSIVE) APHASIA

- EVIDENCE IS MIXED
  - BROMOCRIPTINE (SABE ET AL, 1992; LEEMAN, 2011)
  - AMPHETAMINES (WALKER-BATSON, 2001)
  - BETA-BLOCKERS (BEVERSDORF, 2007)
  - MEMANTINE-WITH CILT (BERTHIER ET AL, 2009)-SMALL RCT
COGNITIVE, BEHAVIORAL, & PHYSICAL

- PERISPINAL ETANERCEPT (TNF INHIBITOR)?
  - RETROSPECTIVE CHART REVIEW OF 617 STROKE & 12 TBI PTS
  - YEARS AFTER INJURY
  - SUBSTANTIAL GAINS IN ALL AREAS

  (TOBI NICK ET AL, 2012)
AGGRESSION SECONDARY TO DISINHIBITION

- EFFICACY OF MOST AGENTS NOT WELL-STUDIED (LEVY ET AL, 2005)
- USE MEDS WITH FEWEST COGNITIVE SIDE EFFECTS
- FIRST WITHDRAW OFFENDING AGENTS: SEE NEXT SLIDE
IRRITABILITY & AGGRESSION INFLUENCED BY MEDICATIONS

- LEVITIRACETAM
- BENZODIAZEPINES: DISINHIBITION
- MEDICATIONS THAT CAUSE SLEEPINESS OR POOR INITIATION (TYPICAL ANTIPSYCHOTICS, SEDATIVES)
- STIMULANTS, DOPAMINERGICS: ESPECIALLY WHEN USED FOR INITIATION OR ALERTNESS PROBLEMS
  - IS IT BETTER TO HAVE A PATIENT WHO DOES NOTHING OR A PATIENT WHO IS DISRUPTIVE OR AGGRESSIVE?
MEDI CATIONS FOR AGGRESSION & IRRITIBILITY

- AMANTADINE (Hammond et al, 2013)
- STIMULANTS, ETC (WHEN DUE TO SLEEPINESS, POOR INITIATION)
- ANTI CONVULSANTS (E.G., VALPROATE, CARBAMAZEPINE, OXCARBAZEPINE, PHENYTOIN) (HUBAND, COCHRANE REVIEW, 2010)
- ANTI DEPRESSANTS (E.G., SSRI’s, TRICYCLICS, TRAZODONE)
- BETA-BLOCKERS (E.G., PROPRANOLOL, PINDOLOL)
- BUSPIRONE
- LITHIUM
MEDITATIONS FOR AGGRESSION & IRRITABILITY

- Atypical Antipsychotics (e.g., Risperidone, Aripiprazole)
  - See next slide

- Typical Antipsychotics (e.g., Haloperidol)
  - May cause global decrease in function

- Benzodiazepines (e.g., Lorazepam, Clonazepam): Can cause disinhibition

- Above can usually be given p.o.
  - Aggressive pts often agree to take
  - IM may exacerbate situation
  - IM still takes time to work—need to deal with situation
ATYPICAL ANTIPSYCHOTICS

- LESS EPS
- LESS TARDIVE DYSKINESIA
- CAN CAUSE
  - DIABETES MELLITUS
  - WEIGHT GAIN
  - HYPERLIPIDEMIA
- CARDIAC ARREST - GET EKG, LOOK FOR QT PROLONGATION
- STROKE
- SEDATION VARIES
- IMPROVE COGNITIVE FUNCTION IN SCHIZOPHRENICS
POST-TRAUMATIC CONFUSIONAL STATE IN THE ICU

- PRIORITY: LIFE & DEATH, MEDICAL STABILITY
- TREAT SLEEP, PAIN, SOMNOLENCE WHEN POSSIBLE
- LOWER MORTALITY ON HALOPERIDOL (5-12.5 MG) IN VENTILATED PTS
  - NOT TBI STUDY
- GET OFF MEDICATIONS AS SOON AS POSSIBLE
AGITATION ON THE REHAB UNIT

- PRIORITIES:
  - PATIENT & STAFF SAFETY
  - REHABILITATION PROGRESS
- TREAT SLEEP, PAIN, SOMNOLENCE
- TAPER & STOP LEVETIRACETAM IF POSSIBLE
- CONSIDER NOT TREATING WITH DRUGS—USE 1:1, NET BED, WAIT
- CONSIDER INCREASING ALERTNESS & ATTENTION WITH AMANTADINE OR STIMULANTS
- MAY NEED TO USE ATYPICAL ANTIPSYCHOTICS FOR DANGEROUS BEHAVIORS, VALPROIC ACID FOR AGGRESSION
- GET OFF MEDICATIONS AS SOON AS POSSIBLE
EMOTIONAL LABILITY & PSEUDOBULBAR AFFECT

- ANTIDEPRESSANTS
- DEXTROMETHORPHAN/QUINIDINE (NUEDEXTA)
SUMMARY

- KNOW WHAT YOU ARE TREATING
- ALL ELSE BEING EQUAL, USE MEDICATIONS WITH FEWEST SIDE EFFECTS, PARTICULARLY COGNITIVE
THANK YOU!