Treatment of treatment resistant anxiety disorders

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Aims of Talk

- Review the different classes and specifics of major anti-depressants groups and how they work of anxiety disorders
- Review the role of atypical anti-psychotics in this population
- Discuss some medications already here and those on the horizon worth knowing about

Consequences of not treating Anxiety and Depression

Six D's of Psychopharmacology

1. Diagnosis
2. Drug
3. Dose
4. Duration
5. Discussion
6. Discontinuation

Is there a role for Benzodiazepines?

- Limited role in limited patients
- Can be helpful if symptoms escalating rapidly
- Role is short term NOT long term
- If history of drug or alcohol abuse/dependence then no should AVOID
- Effective choses include lorazepam and clonazepam NOT diazepam (Valium)
- Each benzo has a sedative(hypnotic)/relaxant/anticonvulsant/anxiolytic properties and no two are alike
- SSRIs as a class have now become the new gold standard for the treatment of Anxiety disorders

Current Classes of Antidepressants

- SSRI'S
- SSNRI's
- NaSSA
- NRI's
- SDRI's
- TCA's
- Other, MAOI, RIMA,etc

SSRI's

- It all began with Fluoxetine (Prozac) and ends with Sonafem or Lovan (Fluoxetine)
- In between them came
  - Paroxetine
  - Sertraline
  - Fluvoxamine
  - Citalopram
  - Escitalopram

Are all SSRI's equal?

- **Fluoxetine**- the first and the longest t1/2
  - 2-3D+7-9D, other SSRIs t ½=24 hours
  - Only one indicated for Bulimia and first for PMS (new name for new indication)
  - Combiation with olanzapine=weight nuetral combination
  - Most activating of all SSRI's
  - Scientology and Michael Hutchins of INXS
- **Paroxetine-** most indications (MDE and all Anxiety Disorders)
  - most side effects, i.e Wt. gain, Sexual Dysfunction, Sweating and Discontinuation (Aropax flu)

Are all SSRI's equal? Cont'd

- **Sertraline**
- Often activating and maybe panicogenic in panic disorder
- Consider for atypical depression
- Consider avoiding in patients with IBS/GI somatic symptoms, agitation, insomnia
- Weight neutral
- May act as partial dopamine reuptake blocker
- Maybe more effective in women than men in PTSD

Are all SSRI's equal? Cont'd

- **Fluvoxamine Facts**
- Consider in mixed anxiety/depression
- Well tolerated in panic and OCD
- May have lower rates of sexual dysfunction- mention studies to prove this
- Associated with more drug interactions
- Avoid in patients with GI somatic complaints
- ?sigma 1 receptors action potentiates response and may help insomnia

Are all SSRI's equal? Cont'd

- **Escitalopram (Lexapro) and Citalopram (Cipramil) Facts**
- Most selective SSRI and possibly better tolerated less sexual dysfunction
- Theory is R-citalopram may interfere with binding of S-citalopram at the serotonin transporter, thus
- ? Twice as potent and
- ? quicker onset
- Data suggesting that escitalopram is better anxiolytic that citalopram

SNRI's (Venlafaxine)

- Used initially for treatment resistant depression
- Treatment of Generalized Anxiety Disorder/Social Phobia
- Recent studies suggest maybe useful in OCD if patient fails 1-2 trials of SSRI and potential benefit in neuropathic pain and fibromyalgia
- Like making a cleaner TCA, without the histamine and Muscarinic actions of older TCAs
- Main side effects –sweating, nausea, constipation, anorexia, vomiting, nervousness, hypertension, sexual dysfunction, tremor, blurred vision not contraindication
- In an attempt to reduce side effect profile newer formulation has been developed ER (extended release)- and does have better side effect profile and less withdrawal
- Does have drug withdrawal phenomena but much reduced with XR formulation
- There is a new 37.5 mg dose, thus not just 75/150mg tablets
- Should monitor blood pressure pre and during treatment

NaSSA (NoraSerSpecAgonist)

- Mirtazapine besides affecting alpha-2-autoreceptors also binds 2 post synaptic receptors
- 5HT-2 ANTAGONIST
- 5HT-3 ANTAGONIST
- Allows for 5HT-1A receptor agonism/stimulation and thus anxiolytic/antidepressant properties while minimising side-effects mediated by the 5HT 2 and 5HT 3 receptors
- Two big side effects sedation (less is more) and wt gain
  - These can each be benefical in the right patient

Others

- SNRI's-reboxetine (Edronax)-often combined with SSRI or NaSSA
- MAOI's - Phenelzine and MAOI diet
- RIMA- no diet but drug interactions
- TCA's still popular, for pain and sleep, a lot of side effects limit it's use-Harold
- Buproprion (Zyban SDRI)
  - Discuss seizure issue and possible role in ADHD
- Alprazolam- triazolobenzodiazepine-only benzo that has antidepressants properties, all others can cause depression

Atypical Anitpsychotics

- Clozapine (Clopine)
- Olanzapine (Zyprexa/Zydis)
- Resperidone (Resperdol/Consta/Quicklets)
- Quitiapine (Seroquel)
- Amisulpride (Solian)
- Arirpiprazole (Abilify)
- Zipradone (Zeldox) Just new to Australia
- Help both positive and negative symptoms and bind serotonin and dopamine receptors

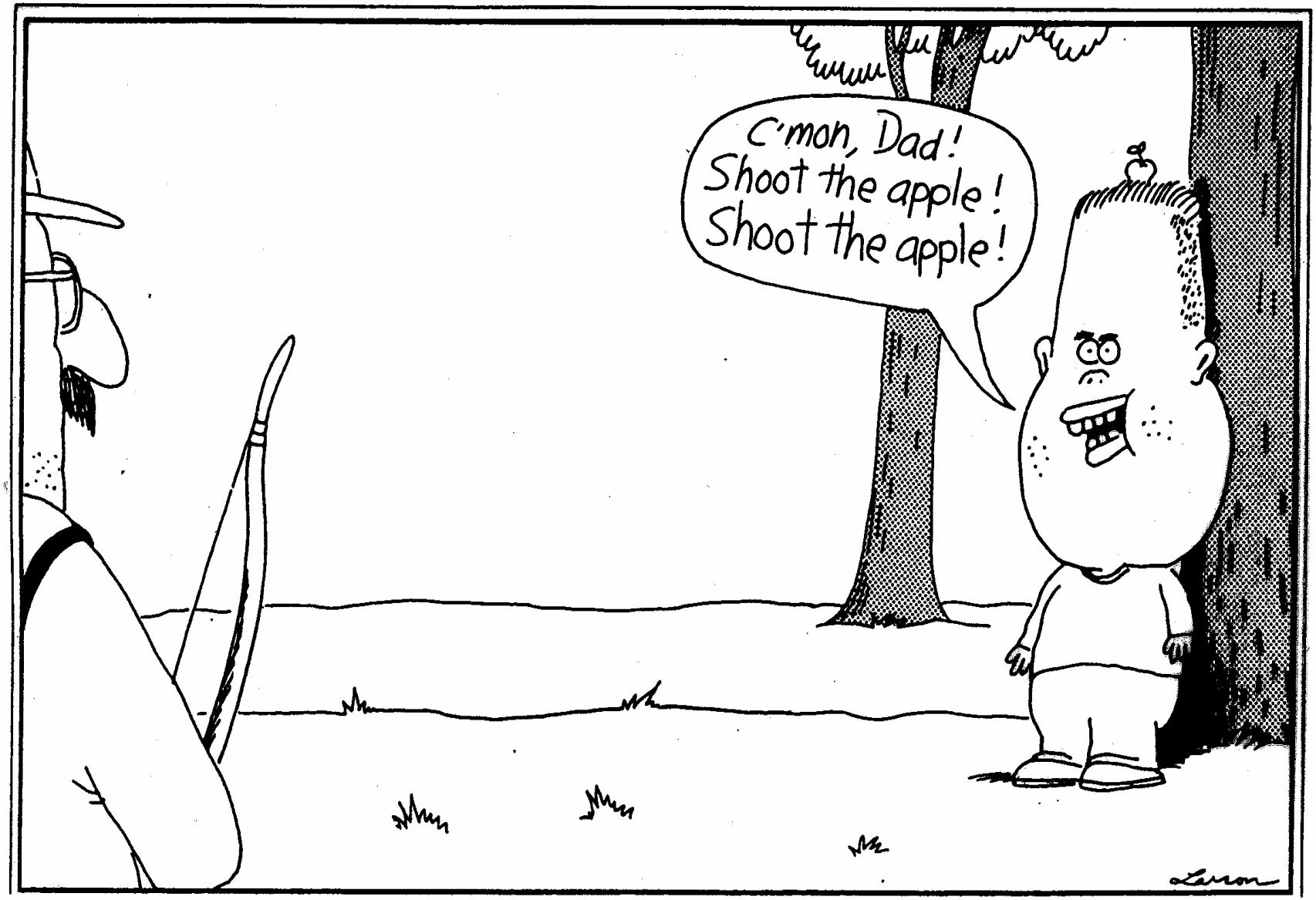
Atypical Anitpsychotics cont'd

- As a class more active in meso-limbic and meso-cortical pathways-led to better clinic response of positive and negative symptoms

- As a class less dopamine binding in the nigro-striatal (assoc with EPSE) and tubero-infundibular pathways thus less effect on prolactin levels

Problems with Atypicals

- Wt. gain
- Diabetes
- Case reports of cardio-myopathy
- Raise lipid levels both triglycerides and cholesterol
- Because of the above the following baseline measurements are now encouraged



Unknown to most historians, William Tell had an older and less fortunate son named Warren.

Baseline Measurements

- -Baseline weight
- -Baseline BMI and waist measurement (at umbilicus)
- -Baseline Blood test esp. fasting glucose, lipids
- -Baseline Blood Pressure
- If any abnormal refer to appropriate medical specialist for review
- At 3 months repeats blood work and BMI and waist measurement (at umbilicus)
- Repeat as necessary in future follow up visits

When to used specific Antipsychotics

Uses of Atypical Antipsychotics

- Psychotic illnesses
- Augmentation of antidepressants when suspicion of co-morbid psychosis
- Augmentation of antidepressants
- All have indication in the US for bipolar maintenance and treatment of manic episodes and soon to follow here
- Only resperidone and olanzapine in Australia with others pending
- Treatment of Severe treatment resistant anxiety disorders

Clozapine

- Treatment Resistant Schizophrenia
- Serious risk of agranulocytosis (Drop WCC)
- Siezures-if occur siezure work-up- if okay consider anticonvulsant
- Hypersalivation
- Has been shown to reduce suicide in patients
- Reports of Cardiomyopathy, so consider baseline echocardiogram

Resperidone

- Growing in popularity again, due to cost effectiveness and availability of new IM Depot CONSTA

May require more benzodiazepine supplementation compared to olanzapine as less sedating

Available in both wafer or oral liquid form as well

Olanzapine

- Popular in "wafer" form in A&E setting
- There is a IM depot that will come to Australia soon
- Antihistamine properties mean ⇑ sedation and weight gain
- In USA there is a combination of Fluoxetine /Olanzapine formulation for severe depression or depressed phase bipolar which is pushed as weight neutral

Qitiapine

- Most prescribed antipsychotic in USA
- Rapid biding and unbinding of receptors may explain lower side effect profile
- Can be sedating in some patients
- Growing in popularity in augmentation of antidepressants and treatment resistant anxiety disorders
- Maybe preferred antipsychotic in Parkinson's Disease

Abilify (Aripiprazole)

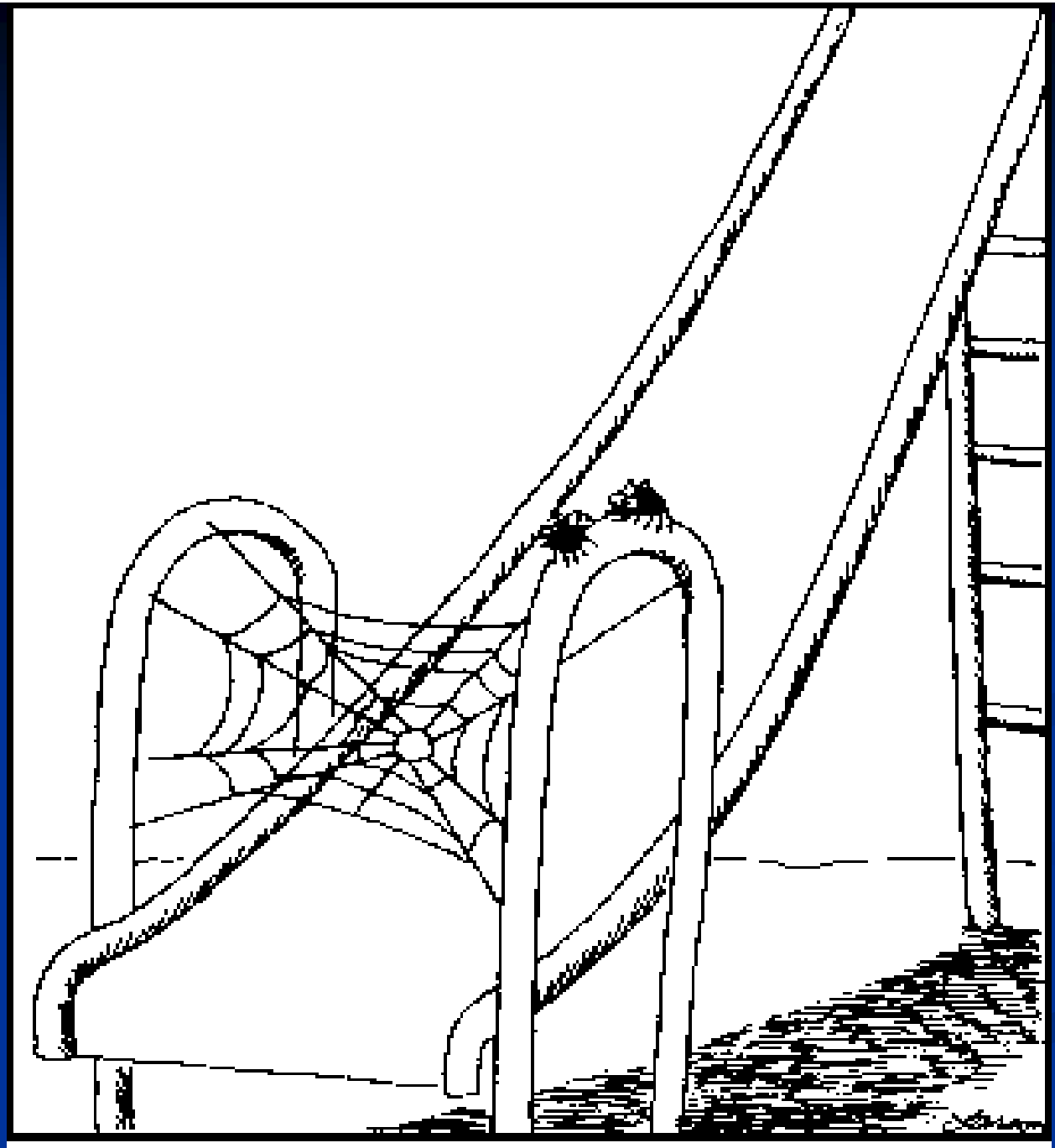
- Unlike other atypicals has different serotonin affinity more for 5-HT-1 that 5-HT-2
- This may explain better side effect profile and possible better antidepressant and anxiolytic possibilities
- Also has agonist/antagonistic properties in the meso-limbic and meso-cortical regions
- Dose range is undergoing rethink like resperidol did in its early days. Now available in 5mg, 10 mg and 15 mg doses. In US new 2 mg dose

Ziprazadone (Zeldox)

- Newest player in the market
- Evidence possible less metabolic risk
- Beneficial for positive and negative symptoms
- Good Bipolar studies
- Dose range 40mg-80mgs 2X day
- More maybe more efficient, but at what cost?

Last but not least

- Stilnox CR-newest version but same product
- Remeltron (Rozerem) first new class of hypnotic in 35 years, acts at the Supra Chiasmatic Nucleus (SCN) helps regulate body clock like melatonin
- Modafanil developed for the treatment of Narcolepsy, but also promising trials in ADHD and possible substance abuse disoders
- Sales in US 1999-25M 2005-575M, no longer just for narcolepsy, US Army has admitted using it in special forces



"If we pull this off, we'll eat like kings."