Autism, Mental Health and Medication:

The Good, The Bad and The ?

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Is ‘Sanity’ Over-Rated?

“Show me a sane man and I will cure him for you.”
— C.G. Jung
Aetiology of Autistic Spectrum Disorders:

Multifactorial – ie, polygenetic and a complex interplay between inherited and environmental factors.
The Multiple Hit Hypothesis of Autism Spectrum Disorders:

EpiGenetics (as defined by Dr. Robin Holliday) are extra-DNA factors capable of influencing the development of mammalian cells through the manipulation of DNA. Dr. Holliday demonstrated that methylation of DNA 'silences' certain genes in both normal and cancer cells.

National Institutes of Health:
http://commonfund.nih.gov/epigenetics/Figure.aspx
Autism and Comorbidities – Including Medical, Psychiatric And Seizure Disorders:

U.S. Centers for Disease Control and Prevention (CDC) reports increased rates of:

Asthma (1.8X)

Eczema or skin allergies (1.6X)

Food allergies (1.8X)

Chronic severe headaches (2.2X)

3.5 X more likely to have gastrointestinal disorders ranging from chronic constipation to diarrhoea or colitis (inflammation of the colon)
Psychiatric and Associated Comorbidities Include:

- Anxiety
- Depression
- Attention-deficit/hyperactivity disorder (ADHD)
- Poor Sleep Hygiene
- Epilepsy
Medications In Autism

Medications Can Be Useful But They Are Just A Tool
“I stopped taking the medicine because I prefer the original disease to the adverse drug reactions.”
Benefit vs Risk
How Much Medication Is Enough?:
‘Rule’ Number One:

• ‘One size DOES NOT fit all’
‘Rule’ Number Two:

• Women during childbearing years are pregnant until proven otherwise (even when on the cocp etc) including those on the autistic spectrum

• THEREFORE: avoid teratogenic medications such as sodium valproate (Epilim)
Molly’s Story:
Molly’s Story:

• Lives in supported accommodation

• Has Down’s Syndrome and is on the autistic spectrum

• Recent increase in assaultive behaviours – police were called twice on the weekend after staff member barricaded herself in the staff office

• Molly presented in the company of a Community Support Worker (who had been part of Molly’s team for a number of years)

• Her demeanour/affect was restricted and anxious (primarily it appears because it was 0945hrs and morning tea is at 1000hrs) – but NO apparent formal thought disorder although only spoke about food and repetitively asked what time morning tea was
Molly’s Story Continued:

**Background:**

Molly is obese and incredibly food focussed

Recent change in staff at her residential home

**Behaviours:** Molly has pinched and pulled at one particular member of staff (the new one) on numerous occasions – this staff member is now afraid of Molly and is refusing to work with her.

Despite the fact Molly has resided at the home for a number of years she is at risk of losing her accommodation.
Molly’s Story Continued:

Request from Management:

Medication review to ‘fix the problem’ OR ELSE she’ll be asked to leave the supported living facility
Molly’s Story Continued:

The ‘pattern’ of violence:
Always around meal times

Starts with incessant asking of ‘what time is teatime’ then if ‘needs not met’ she ‘shadows’ the staff member, starts to pull at their arm and stop them then crescendos to pinching and dragging them.

Molly (although short) is obese and the member of staff is petite – also other staff members find her ‘difficult’

She has always demonstrated ‘challenging behaviours’ when ‘needs not met’ but never as extreme as those she is currently displaying
Molly’s Story Continued:

‘Triggers’:
Molly’s Story Continued:

‘Triggers’: 

It Was Highly Probably That Molly’s Behaviours’s Were More Of A Meltdown Than A ‘Tantrum’
Plan:

• NO change in medications (therefore, NO side-effects etc)

• Education of staff – eg, she is very ‘concrete’ her thought processing so NOT knowing what time ‘teatime’ is, is very anxiety provoking so specifying the time and adhering to it as much as possibly will reduce her anxieties and minimize her assaultive behaviours (new staff member’s response to her questions were vague and non-specific eg, ‘soon’ etc)

• Visual card for Molly – one side: anxious Molly and on the reverse side a picture of Molly wearing head phones listening to her favourite music and looking happy 😊
Andrew’s Story:
Andrew’s Story:

• Lives alone (lived with family until recently – they relocated and he remained) – isolated (recent attempt at flatting failed)

• Works part-time fixing computers

• Recent 2X adx and dx from hospital with psychosis NOS +/- depression

• Most recent dxed home on paliperidone – epse++, erectile dysfunction etc etc (admitted after seeing clouds ‘making funny shapes’ on the way to cooking skills class (interestingly clouds dissipated after to talking with someone on the phone and returning home)

• Family concerned he may harm others and/or commit suicide

• Hates storms (and one is brewing)
Andrew’s Story Continued:

• Most recently he was fixated on the belief that Jesus told him to ‘pour’ water on his Father’s feet (while he was asleep) to ensure his salvation – after 48hrs of reading the bible solidly as had looked up a site on devil worship and believed he was going to ‘hell’ as punishment

• Family concerned about his ‘danger to others’ due command hallucinations – interestingly when I asked him would he punch his Dad in the face if Jesus told him too – he appeared surprise and said ‘of course not’ that would be wrong
Andrew’s Story Continued:

• Very concrete young man with limited supports and coping strategies

Plan:
Complicated as already started on paliperidone and hence be default has a dx of schizophrenia
Anna’s Story:
Anna’s ‘Passion’/’Obession’
Anna’s Story:

• Lives with Mum

• Spends much of day on her computer watching ‘one direction’

• Recently discontinued antidepressant and antipsychotic tx (fluoxetine and olanzapine as unable to masturbate when watching ‘one direction’) – Mum concerned as Anna is 27-yo
John’s Story:
John’s Story:

• Lives in supported accommodation

• Non-verbal

• Recent increase in deliberate self-injurious behaviours (especially biting of arms)

• Now requiring a two person special
John’s Story Continued:

Apart from a recent flu-like illness no obvious precipitants to increased biting

On multiple psychiatric medications including methotrimeprazaine (which is an antipsychotic but prescribed a number of years ago for agitation/self injurious behaviours with good effect)
John’s Story Continued:

Brought into psychiatric emergency in two person restraint – dose of methotrimeprazine increased from 25mg to 50mg

Unfortunately his biting continued to escalate and hence further dose increases were required

14 days after his initial presentation it was noted that John was passing small amounts of rusty coloured urine
John’s Story Continued:

One month are first presenting John died from acute tubular necrosis (renal/kidney failure) secondary to neuroleptic malignant syndrome.

Although we will never know because he was non-verbal it is possible that his escalating self-injurious biting was in the context of ‘painful’ muscles (ie, neuroleptic malignant syndrome induced rhabdomyolysis) – hence increasing doses of neuroleptics such as methotrimeprazine was likely contributing to/driving the behaviours
Potentially Life-Threatening Drug Interactions:
<table>
<thead>
<tr>
<th>SERIOUSNESS</th>
<th>AUTONOMIC SIGNS</th>
<th>NEUROLOGICAL SIGNS</th>
<th>MENTAL STATUS</th>
<th>OTHER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>• Afebrile or low-grade fever</td>
<td>• Intermittent tremor</td>
<td>• Restlessness</td>
<td>• As above</td>
</tr>
<tr>
<td></td>
<td>• Tachycardia</td>
<td>• Akathisia</td>
<td>• Anxiety</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mydriasis</td>
<td>• Myoclonus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Diaphoresis or shivering</td>
<td>• Mild hyperreflexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>• Increased tachycardia</td>
<td>• Hyperreflexia</td>
<td>• Easily startled</td>
<td>• Rhabdomyolysis</td>
</tr>
<tr>
<td></td>
<td>• Fever (up to 41°C)</td>
<td>• Inducible clonus</td>
<td>• Increased confusion</td>
<td>• Metabolic acidosis</td>
</tr>
<tr>
<td></td>
<td>• Diarrhea with hyperactive bowel sounds</td>
<td>• Ocular clonus (slow continuous lateral eye movements)</td>
<td>• Agitation and hypervigilance</td>
<td>• Renal failure</td>
</tr>
<tr>
<td></td>
<td>• Diaphoresis with normal skin colour</td>
<td>• Myoclonus</td>
<td></td>
<td>• Disseminated intravascular coagulopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(secondary to hyperthermia)</td>
</tr>
<tr>
<td>Severe</td>
<td>• Temperature often more than 41°C (Secondary to increased tone)</td>
<td>• Increased muscle tone (lower limb &gt; upper)</td>
<td>• Delirium</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Spontaneous clonus</td>
<td>• Coma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Substantial myoclonus or hyperreflexia</td>
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Data from Boyer and Shannon.⁴
Stopping the broken record/ruminating thoughts

- ‘Reframing’ is a term used to describe psychological strategies to modify negative (and at times derogatory) ‘self-talk’ into more positive and constructive thought processes and is an important non-pharmacological tool.

- Risperidone is considered an ‘antipsychotic’ drug which is used ‘off label’ as an ataractic agent to dampen maladaptive/antisocial and at times violent behaviours in autistic individuals.

- Anxiolytics are central nervous system (CNS) depressants. They include medications which increase gabaminergic activity (GABA – the main inhibitory neurotransmitter in the brain) and/or decrease glutamate activity (the main excitatory neurotransmitter in the brain). Other less commonly used anxiolytics include anti-histamines (H₁) such as quetiapine and buspirone.

  n.b. these medications may require much smaller or larger doses for individuals on the AS compared with other populations.
Depression

Being on the AS is a risk factor for experiencing depression.
‘Multiple-Hit’ Hypothesis of Psychopathology (Such As Depression):

- Mental ‘Wellness’
- Current Psychosocial Stressors Including Death of a Family Member, Divorce and/or Loss of a Job
- Genetic Loading
  - Other Coexisting factors which may increase the risk of social isolation including Autistic Spectrum Disorders.
- Social Supports Network Vs Social Isolation
- Chronic Pain and Other Physical Comorbidities
- Coping Strategies Including Lack Of and/or Maladaptive Such As Alcohol and Other Substances of Abuse.
- Other Environmental Factors Including Gender, Sexual and/or Racial Discrimination etc
- Mental ‘Illness’
- Childhood Adversity
- Current Psychosocial Stressors Including Death of a Family Member, Divorce and/or Loss of a Job
Monoamine hypothesis of depression.

↓ serotonin (5HT)  ↓ noradrenaline (NA)

Monoamine hypothesis = insufficient levels of NA and/or 5HT in the CNS is causing the symptoms associated with depression.

1. NE = Norepinephrine (US). NA = noradrenaline in UK/Australasia etc
2. 5-HT = Serotonin
3. SERT = Selective-Serotonin-Reuptake-Transporter
Types of antidepressants

- Tricyclics
- Selective Serotonin Reuptake Inhibitors (SSRIs)
- Monoamine oxidase inhibitors (MAOIs)
- Others eg, venlafaxine (SNSRI)
SSRI’s Versus Tricyclic Antidepressants (TCA)

• SSRIs such as fluoxetine and citalopram have a ‘wider’ therapeutic Index (ie, they are safer than TCA in overdose).

• TCA are generally more sedating due to histamine-1 (H₁) receptor antagonism (however, this can also be ‘harnessed’ as a therapeutic benefit in patients where sleep is problematic).

• Also, TCA tend to cause less sexual dysfunction so appear to be better ‘tolerated’ by males.

• Less anticholinergic and α₁ antagonism with SSRIs (compared to TCA).
Common Side-Effects Associated With SSRIs:

- Gastrointestinal
- Sexual dysfunction
- Central Nervous System

Effects on the GI tract:
- Stimulation of 5-HT3R & 5-HT4R
- Increased GI motility, GI cramps
- Diarrhea

Nausea and vomiting:
- 5-HT3R: Hypothalamus, Brainstem (CTZ)
CNS/Mental side effects generally occur in the early phase of medication initiation and are believed to arise from stimulation of 5HT$_{2A}$ and 5HTC receptors resulting in mental agitation, anxiety and panic attacks. Hence ‘starting low and going slow’ coupled with good patient education can help reduce patient distress/fear and minimise the risk of non-compliance with medications.
Sexual dysfunction including diminished libido, anorgasmia, impotence and delayed ejaculation is a common reason for antidepressant (especially SSRIs) non-compliance particularly in males.
Anti-psychotics and the AS

• These are often used for helping to manage aggressive behaviour and/or for severe anxiety

First Generation Antipsychotics

D2 Antagonism

Higher risk of neurological side effects

Second Generation Antipsychotics

• 5HT2A/D2 antagonism

Higher risk of metabolic side effects
Risperidone - Prescribing Facts

Dosage range:
- 2 – 8 mg/day for acute psychosis and bipolar disorder
- 0.5- 2 mg /day for children and elderly patients
- 25-50 mg IM every two weeks

Approved for use in children and adolescents:
- Schizophrenia, ages 13 and older
- Acute mania/mixed mania, ages 10 and older
- Autism related irritability in children, ages 5 -16

LAI approved for maintenance treatment of bipolar 1 disorder

Risperidone - side effects

Weight gain: intermediate risk.
  Lower risk than olanzapine and clozapine
  Higher risk than aripiprazole and ziprasidone

EPS risk is dose dependent.
  A PET study found that risperidone occupies 75-80% of striatal D₂ receptors at a dose of 6mg/day.

Prolactin elevation is a risk++++++++++
Paliperidone

- Metabolite of risperidone: 9-hydroxyl-risperidone
- Available as LAI: paliperidone palmitate

Dosage range: 6 mg/day (up to 12 mg/day)

Dosage forms:
  - Extended release tablets: 3 mg, 6 mg, 9 mg
  - LAI - Paliperidone palmitate: 39 mg, 78 mg, 117 mg, 156 mg, 234 mg.

- First antipsychotic to be approved for schizoaffective disorder.
- Paliperidone and risperidone are the two SGAs associated with hyperprolactinemia.

Mood stabiliser - Quetiapine

Approved for:

- Bipolar maintenance (mood stabilizer)
- Acute mania/mixed states
- Adjunctive treatment of MDD

Adverse effects:

Most common adverse effects: somnolence due to $H_1$ receptor antagonism, orthostatic hypotension due to $\alpha_1$ blockade inhibiting total peripheral resistance (TPR), weight gain (moderate risk).

EPS is low risk (as less $D_2$ antagonism compared with typical antipsychotic medications). Drugs like quetiapine are safer in patients with Parkinson’s disease because minimal $D_2$ blockade.

Continuum of Relative $t^{1/2}$ and Dosage For Commonly Prescribed Benzodiazepines:

- **Triazolam**
  - $t^{1/2}$: 1.6 – 5.5 hrs
  - Dose: 0.5mg

- **Midazolam**
  - $t^{1/2}$: 1 – 4 hrs
  - Dose: 15mg

- **Temazepam**
  - $t^{1/2}$: 10 – 20 hrs
  - Dose: 30mg

- **Oxazepam**
  - $t^{1/2}$: 3 – 21 hrs
  - Dose: 15mg

- **Lorazepam**
  - $t^{1/2}$: 10 – 20 hrs
  - Dose: 1mg

- **Clonazepam**
  - $t^{1/2}$: 18 – 39 hrs
  - Dose: 0.25mg

- **Alprazolam**
  - $t^{1/2}$: 6 – 20 hrs
  - Dose: 0.5mg

- **Diazepam**
  - $t^{1/2}$: 20 – 50 hrs Dose: 5mg

- **Diazepam and Active Metabolites**
  - $t^{1/2}$: 3 – 100 hrs Dose: 5mg

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