Haloperidol vs Olanzapine
From Stain to Brain

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Haloperidol vs Olanzapine

• Discovery of Antipsychotics
• Haloperidol Pharmacology
• Olanzapine Pharmacology
• Antipsychotics in Practice
19th Century – Age of the British Empire
Risk to Britain’s colonialists of exposure to malaria increased
Relief available for malaria – quinine
Extracted from the bark of the *cinchona tree*
- from the remote eastern slopes of the Andes
- expensive and difficult to get hold of
- the Dutch managed to grow the plants in their Indonesian plantations
• William Henry Perkin – student chemist
• 1856 - set out to develop a synthetic quinine using coal tar extracts
• At the end of the experiment, what he got was a muddy, black mess!
• Cleaned up the failed experiment with alcohol
  – sludge turned bright purple
  – stained everything it touched
• Serendipitously created a synthetic purple dye
• Mauveine used in products ranging from stamps to clothes
• Google produced a Doodle this year (12th March) to celebrate his 180th birthday
• His discovery set off a chain of events that would eventually lead to the development of antipsychotic drugs
• Other dye products developed
• 1876 – Heinrich Caro
• Synthesised a pure blue dye for cotton
  – methylthioninium chloride
• Paul Ehrlich – Father of Chemotherapy
• In 1891, Ehrlich successfully used the blue dye to treat two patients with malaria
  – first ever use of a synthetic drug in medicine

Discovery of Phenothiazines

Methylene blue

\[
\text{Methylene blue} \quad \text{Cl}^{-}
\]
Discovery of Phenothiazines

- WW1 – Germans cut off from the primary supplies of quinine
- Following WW1, Bayer synthesized additional compounds related to methylene blue
- 1928 – discovered mepacrine
- Mepacrine and quinine provided primary treatment for malaria until WW2
- WW2 – Allies denied access to quinine and mepacrine
- Rhône-Poulenc Laboratories studied derivatives of methylene blue
- Phenothiazine derivatives were inactive antimalarials
- Investigated for other commercial uses
- 1947 – promethazine introduced
Discovery of Phenothiaazines

- Search for other phenothiazine derivatives with similar activity
- 1950 – chlorpromazine synthesized
- 1951 – serendipitously given to psychiatrists to try on psychotic patients
- 1952 – marketed as Largactil
Belgian company, led by Paul Janssen, established as manufacturer of Palfium (dextromoramide)

Janssen wanted to develop more powerful analgesics than dextromoramide

Synthesised by-products of pethidine, arriving at the first butyrophenone

1958 - haloperidol represented the 45th synthesised by Janssen

Was a poor analgesic but induced cataleptic state and a sedation close to that provoked by chlorpromazine
Five weeks after synthesis, human trials started!
Two random patients received haloperidol
Janssen felt that serendipity played a part in the outcome of these first real trials of haloperidol
Based on the success in the two patients clinical trials of haloperidol on psychotic patients initiated
Marketed in Belgium in 1959/US 1969
1994 - 35 years following its launch, more than 250 million people were treated with haloperidol
The first generation antipsychotics (FGAs) were associated with adverse effects, in particular extra pyramidal symptoms (EPS) such as Parkinsonism.

- Research to find cleaner drugs led to discovery of imipramine.
- 1959 – clozapine synthesized.
- Serious flaws in the animal tests; had they been repeated, clozapine would have been discarded!
- Showed similar efficacy to earlier treatments but without the range of EPS.
- Clinical experience soon destroyed the belief efficacy and EPS profile were linked.
• Agranulocytosis identified in 1975
• 1989 – introduced in UK
• Strict blood monitoring programme

• “Atypical” antipsychotics introduced
  – low propensity to induce EPS
  – unrelated to FGA chemical structures
  – drugs post-clozapine
• Second generation antipsychotics
• Success of clozapine stimulated development of other atypical antipsychotic drugs
• Olanzapine developed by Lilly and based on clozapine
• During early development, in-vitro binding studies were unavailable; behavioural studies were used instead
• Olanzapine was as beneficial as clozapine (unlike haloperidol) and five times as potent
• Serendipity - had binding studies been a primary method of selecting compounds, it is unlikely olanzapine would have been developed!
Antipsychotic Pharmacology
Pharmacology of Haloperidol

- Butyrophenone antipsychotic
- Selectively acts via dopamine D₂ receptors
- Some effect at α₁-adrenoreceptors
- Minor activity at H₁ and 5-HT₂ receptors
- Also binds to σ₁-receptor\(^{(1)}\)
  - originally misclassified as one of the opioid receptors
  - no clear endogenous ligand has been identified
  - modulates opioid and NMDA receptors
  - antinociceptive effect?

Pharmacology of Haloperidol

- Oral bioavailability 44-75%
- First-pass metabolism in the gut
- PO to SC/IM haloperidol ratio of 3:2 suggested
  - i.e. 3mg oral = 2mg SC
- Extensively metabolised by CYP3A4 and CYP2D6
  - minor pathway involves CYP1A2
- Is an inhibitor of CYP2D6
- Variety of metabolites – some active
- Haloperidol has a long half-life which can permit a once-daily SC dose.
Pharmacology of Olanzapine

• Second generation antipsychotic
• Antagonises a wide range of receptors in producing its antipsychotic therapeutic effects
• Antagonises additional receptors that explain the range of effects that are produced
  – H₁ sedation & appetite
  – 5-HT₂c weight gain/metabolic effects
  – 5-HT₃ antiemetic
• D₂/5HT₂A antagonism explains reduced EPS
Pharmacology of Olanzapine

- Well absorbed after oral administration 60-80%
- Mainly metabolised in the liver by glucuronidation
- CYP1A2 involved to a lesser degree
- CYP2D6 has a minor role
- The main metabolite of olanzapine is inactive.
In Practice

Olanzapine

Haloperidol
Haloperidol Indications

1. Psychosis
2. Delirium
3. Intractable hiccup
4. Aggression and psychotic symptoms in patients with moderate to severe Alzheimer's and/or vascular dementia
5. Restlessness and agitation in the elderly
6. Nausea and vomiting
   - especially if CTZ affected
   - e.g. drugs, renal failure
7. Terminal agitation

What's it used for?

a) when non-pharmacological treatments have failed
b) when non-pharmacological treatments have failed and when there is a risk of harm to self or others; oral solutions only indicated
Olanzapine Indications

What’s it used for?

1. Psychosis
2. Delirium\(^a\)
3. Nausea and vomiting
   - CINV
   - refractory
4. Terminal agitation

\(^a\) when non-pharmacological treatments have failed
Haloperidol Contra-Indications

1. Parkinson’s disease
2. Lewy Body dementia
3. Elderly with dementia
4. Known QTc interval prolongation or congenital long QT syndrome
5. Recent acute myocardial infarction
6. Uncompensated heart failure
7. History of ventricular arrhythmia or torsades de pointes
8. $K^+ \downarrow\ Mg^{2+} \downarrow$
9. Drugs affecting QT
1. Glaucoma
Haloperidol Precautions

1. Cardiac disease
2. Diabetes (low risk of metabolic disturbances)
3. Hepatic impairment
4. Epilepsy (lower risk)
5. CYP2D6/CYP3A4 inhibitors
1. Cardiac disease
   • $K^+ \downarrow$  $Mg^{2+} \downarrow$
2. Diabetes
3. Parkinson’s disease
4. Lewy Body dementia
5. Dementia-related psychosis
6. Hepatic/renal impairment
7. Drugs affecting QT
8. Epilepsy (higher risk)
9. Smoking (CYP1A2)
<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Mechanism</th>
<th>Haloperidol</th>
<th>Olanzapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPS</td>
<td>$D_2$</td>
<td>++++</td>
<td>+</td>
</tr>
<tr>
<td>Sexual dysfunction (↑ prolactin)</td>
<td>$D_2$</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>$\alpha_1$</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>VTE</td>
<td>Unknown</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>CVA</td>
<td>Unknown</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Dry mouth/constipation</td>
<td>$M_{1-3}$</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>$H_1$</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Lowered seizure threshold</td>
<td>Unknown</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Weight gain</td>
<td>$H_1$ $5\text{HT}_{2C}$</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Type II diabetes mellitus</td>
<td>$M_3$ Other</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>Unknown</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>
Drug Interactions

- Reduced action of drug(s)
- Increased action of drug(s)
- Adverse effects
Haloperidol Interactions

Avoid

Drugs known to prolong the QTc interval:
- Amiodarone
- Citalopram
- Clarithromycin
- Domperidone
- Erythromycin
- Methadone
- Quinine
Haloperidol Interactions

- **CYP3A4 inducers**
  - carbamazepine, phenobarbital, phenytoin, rifampicin
  - can reduce concentrations by 50%

- **CYP3A4 inhibitors**
  - clarithromycin, erythromycin, itraconazole
  - risk of toxicity

- **CYP2D6 inhibitors**
  - fluoxetine, paroxetine
  - risk of toxicity
Drugs known to prolong the QTc interval:

- Amiodarone
- Citalopram
- Clarithromycin
- Domperidone
- Erythromycin
- Methadone
- Quinine
Olanzapine Interactions

- Sudden cessation of smoking can increase exposure
  - CYP1A2
Concerns

- Haloperidol
- Olanzapine
- D1
- D2
- D3
- 5HT2a
- 5HT2c
- 5HT3
- 5HT6
- SHT7
- M1
- H1
- M2
- 5HT7

- VTE
- Dementia
- QTc
Mounting evidence suggests a causal link between antipsychotic (AP) drug use and the occurrence of VTE.

Meta-analysis estimated ≥50% VTE risk\(^1\).

There is no pharmacological explanation.

It is not associated with:

- metabolic abnormalities
- sedation
- hyperprolactinemia

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Venous Thromboembolism

- SPC
  - Haloperidol unknown
  - Olanzapine uncommon (0.1 – 1%)

- Risk applies to ALL antipsychotic drugs
- Inconclusive data on individual antipsychotics
- Consider the risk factors for VTE when initiating
- Highest risk of VTE emerges during the first 3 months
• Over 35m people have dementia worldwide
• Anticipated to double every 20 years
  – 131 million worldwide by 2050
• Behavioural and psychological symptoms of dementia (BPSD) experienced by up to 80%
  – anxiety, depression, agitation, aggression, delusions, hallucinations
• Pharmacological and non-pharmacological treatments
• Antipsychotics have been shown to cause an increased incidence of severe adverse effects in people with dementia.
• An increased risk of mortality has been consistently observed in elderly patients with dementia treated with antipsychotics.
• Cause of mortality - CV and pneumonia
  — mechanism unknown
• Evidence of individual drug risks is conflicting
• Greatest risk within first month and higher doses
• QT prolongation remains the best marker for risk of TdP and ventricular arrhythmia
• QTc is prolonged if > 440ms in men or > 460ms in women
• Absolute risk of a catastrophic event with a QTc of 600ms remains less than 1 in 4000
All antipsychotics carry a risk
Haloperidol seems to carry higher incidence:
   - IV
   - greater use
Evidence for clinically meaningful QT prolongation with most classes of antipsychotics remains minimal
Evidence suggests that >85% of patients with drug-induced QTc prolongation have two or more additional risk factors.

Drug-induced QT interval prolongation is dose and route related and uncommon at doses typically used in PC.

Watch out for drug interactions.
• NG97; June 2018
• Agitation, aggression, distress, psychosis
• Explore and address reasons for distress
• Only offer antipsychotics if the person is:
  – at risk of harming themselves or others
  – experiencing agitation, hallucinations or delusions that are causing them severe distress
• Use the lowest effective dose for the shortest possible time
• Reassess at least every 6 weeks
Antipsychotics - Dementia

- Canadian algorithm for BPSD associated with AZH/vascular dementia recommends SGA over FGA(1)
- Olanzapine **not** recommended due to metabolic adverse effects
- Haloperidol **not** recommended since risk both of death and femur fracture greater than vs SGA

• Use of antipsychotics to treat BPSD should be confined to those with only the severest symptoms in view of the significant risks

• Haloperidol (liquid) is licensed for use in AZH and/or vascular dementia
  – when non-pharmacological treatments have failed and when there is a risk of harm to self or others; oral solutions only indicated
Delirium: prevention, diagnosis and management

- CG103
- Published 2010; updated 2015
- Identify and manage the possible underlying cause(s)
  - constipation, dehydration, hypoxia, infection, medication, pain
- Haloperidol or olanzapine are suggested treatments when person
  (i) with delirium is distressed
  (ii) is considered a risk to himself or others when verbal and non-verbal de-escalation techniques are ineffective or inappropriate
Efficacy and tolerability of atypical antipsychotics in the treatment of delirium: A systematic review of the literature

Rivière et al. Psychosomatics 2018 [Epub 21st May 2018]

- Haloperidol is the most widely used drug in the treatment of delirium
  - minimal anticholinergic and sedative effects
- Olanzapine “seems” to be adequate alternative to haloperidol:
  - at risk of EPS
  - require sedation
  - history of haloperidol intolerance
- Larger-scale RCTs are urgently required to compare olanzapine/haloperidol/placebo
Antipsychotics - Delirium

Efficacy and side effect profile of olanzapine versus haloperidol for symptoms of delirium in hospitalized patients with advanced cancer: A multicenter, investigator-blinded, randomized, controlled trial

Van Der Vorst et al. Palliat Med. 2018; 32(1_Suppl):8

- Presented at EAPC 2018
- Hypothesised olanzapine more effective and better tolerated than haloperidol
- Olanzapine (n=50) haloperidol (n=50)
- No difference in efficacy or side effect profile was observed
- Choice determined by adverse effect profile rather than efficacy
Evaluating the Current Evidence for the Pharmacological Management of Delirium in Adult Cancer Patients

- Presented at EAPC 2018
- 581 citations identified
- 2 RCTs; only 1 had placebo arm; 4 cohort studies
- Evidence for antipsychotics in management of delirium is variable
- Use judiciously
Antipsychotics – Nausea/Vomiting in Palliative Care

- No RCTs
- No head:head comparisons
- Haloperidol
  - insufficient evidence to determine effectiveness for nausea and vomiting in palliative care¹
  - phase IV pharmacovigilance study reported provided rapid net clinical benefit with low-grade, short-term harms²
- Olanzapine
  - limited to case reports³ or series⁴

Efficacy of haloperidol versus olanzapine for control of chemotherapy induced nausea and vomiting.


• Compared efficacy & toxicity in prevention of CINV in patients receiving highly emetogenic chemotherapy
• Patients randomised to receive olanzapine (10mg PO; n=30) or haloperidol (1mg PO; n=30) on days 1-4
  – all got ondansetron 16mg OD and dexamethasone 12mg IV on day 1
• No statistical difference between groups
Olanzapine for the prevention and treatment of cancer-related nausea and vomiting in adults (Review)

Sutherland A, Naessens K, Plugge E, Ware L, Head K, Burton MJ, Wee B
Olanzapine for the prevention and treatment of cancer related nausea and vomiting in adults (Review)


- Olanzapine probably doubles the likelihood of no nausea or vomiting during chemotherapy from 25% to 50%
- Uncertain if olanzapine increases the risk of serious adverse events but may increase other adverse events.
CSCI Administration

• Haloperidol:
  – no RCTs; case series
  – alfentanil, clonazepam, cyclizine, diamorphine, fentanyl, glycopyrronium, hydromorphone, hyoscine butylbromide, hyoscine hydrobromide, ketamine, methadone, metoclopramide, midazolam, morphine, oxycodone and tramadol

• Olanzapine:
  – no published evidence for administration via CSCI
  – manufacturer recommends solution used within 1 hour
  – no data; based on USP “sterile preparations”
  – anecdotal reports suggest CSCI well tolerated
  – midazolam