Role of psychotropics in suicide prevention

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Dr Kate Saunders
Clinical Lecturer & Consultant Psychiatrist
Centre for Suicide Research
University of Oxford
Overview

• Background & methodological issues
• Lithium
• Anticonvulsants
• Antipsychotics
• Antidepressants
• Ketamine
• Minor tranquillisers
• BPD
Background

• Suicide rare but devastating event
  • 11/100,000 /year internationally but rates vary considerably
• In the top three causes of death in those aged 15-44 (WHO)
• Suicide is strongly associated with mental disorder
  • Major affective disorders predominate
  • SMR = 10-20x general population
Methodological challenges

• Large numbers
• Ethics of recruiting suicidal patients
• Role of concomitant factors e.g. substance misuse
• Nomenclature
• Need to control for frequency of clinical contact
• Commercial considerations

• Evidence largely observational or from post hoc analyses
Lithium
Rx for bipolar disorder
Augmentation in UD

Meta analysis of RCTs
Cipriani 2013 BMJ
Suicide attempts

• Registry based study

• 826 hospitalised bipolar patients

• Lithium
  • Lower risk of suicide attempts (non significant)
  • Lower risk of suicide (univariate RR=0.39, p=0.03, cox HR=0.37, p=0.02)
  • Decreased all cause mortality by 49%
Self-harm, Unintentional Injury, and Suicide in Bipolar Disorder During Maintenance Mood Stabilizer Treatment
A UK Population-Based Electronic Health Records Study

Joseph F. Hayes, MSc, MBChB; Alexandra Pimlott, PhD; Louise Marston, PhD; Kate Walkers, PhD; John R. Geddes, MD; Michael King, PhD; David F. J. Osborn, PhD

Shown are unadjusted Kaplan-Meier estimates of cumulative self-harm, with shaded areas showing 95% CIs.
Studies on the potential anti-suicidal effects of lithium as a trace element in drinking water

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Measurement</th>
<th>Number of samples</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>Japan</td>
<td>Li level in drinking water</td>
<td>18 municipalities</td>
<td>Standardized mortality ratio (SMR) negatively correlated with Li levels</td>
</tr>
<tr>
<td>2011</td>
<td>UK</td>
<td>Li level in drinking (tap) water</td>
<td>47 samples from 47 subdivisions</td>
<td>No association between lithium levels in drinking (tap) water and mortality from suicide in the East of England</td>
</tr>
<tr>
<td>2011</td>
<td>Austria</td>
<td>Li level in drinking water</td>
<td>6460 lithium measures of 99 Austrian districts</td>
<td>Suicide rate, SMR inversely associated with Li levels</td>
</tr>
<tr>
<td>2013</td>
<td>Greece</td>
<td>Li level in drinking water</td>
<td>149 water samples from 34 prefectures</td>
<td>Tendency for lower suicide rates in the prefectures with high levels of lithium in drinking water</td>
</tr>
<tr>
<td>2013</td>
<td>USA</td>
<td>Li level in public water</td>
<td>3123 lithium water samples, 226 counties</td>
<td>Higher lithium levels in the public drinking water were associated with lower suicide rates</td>
</tr>
<tr>
<td>2015</td>
<td>Italy</td>
<td>Li level in drinking water</td>
<td>Review</td>
<td>Higher levels in drinking water may be associated with reduced risk of suicide in the general population</td>
</tr>
</tbody>
</table>

Li: lithium
Lithium – mechanism of action

• Unknown
• Greater magnitude of effect on suicidality than depressive Sx

BUT
- Narrow therapeutic window
- Significant side effects
- Highly toxic in overdose
Anticonvulsants

- Rates of suicide may be higher in those on sodium valproate (Goodwin 2003, Toffol 2015)
  - Confounding by indication
  - Increased risk associated with stopping lithium to switch to valproate

- No difference between anticonvulsants & lithium reported (Yerevanian 2003)

- Danish data suggest protective effect if compliant (Smith 2009)
  - Large sample
  - Healthcare records
  - Consistent collection of prescriptions associated with reduction in suicides
  - Similar reduction for lithium
Antipsychotics

• In RCTs little difference found when compared to placebo (Khan 2001)
  • All FDA registered trials of FGA or SGA v placebo
  • May simply reflect sample characteristics of those entering RCTs
• Retrospective database study suggested better compliance reduced risk

• Available data supports the protective effect of Clozapine
  • Those switched to clozapine demonstrated a reduction in suicide attempts (Meltzer 1995)
    • No follow-up data reported

• Clozaril National Register (62,072 patients) – current users had lower mortality rate than past users
  • No control group
  • Discontinuation associated with poorer clinical outcome
Intersept (International Suicide Prevention Trial)

- Olanzapine v Clozapine
- Randomised multicentre trial
- Schizophrenia / Schizoaffective
- 980 patients
- 18 months
- Fewer suicides but small N
Clozapine - mechanism

• Closer follow-up due to monitoring for agranulocytosis
• Better symptomatic control
• Unique and complex pharmacology
  • Simultaneous modulation of multiple neurotransmitters
  • Hormones e.g. cortisol
  • Intracellular systems e.g. NMDA receptor expression
Antidepressants

• Controversial issue

• Ongoing debate especially in young people
  • Suicide 3rd leading cause of death in young people
  • 90% of depressive symptoms untreated at time of death (Leon 2004)
Impact of safety warnings

USA

Netherlands

Gibbons AMJ Psych 2007
BMJ 2014
Healthcare claims data
11 health plans un the
US mental health
research network
Adolescents (10-17)
Antidepressants

Table 2  Fatal toxicity: rate ratios and relative toxicity indices for individual antidepressants based on rates of death (suicide and undetermined intent) in England and Wales, and prescription rates in the UK

<table>
<thead>
<tr>
<th></th>
<th>Both genders</th>
<th></th>
<th>Males</th>
<th></th>
<th>Females</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Rate ratio</td>
<td>Relative toxicity index</td>
<td>Rate ratio</td>
<td>Relative toxicity index</td>
<td>Rate ratio</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td></td>
<td>(95% CI)</td>
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<td>(95% CI)</td>
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<tr>
<td>TCAs</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Amitriptyline</td>
<td>11.4 (10.3–12.6)</td>
<td>1.0</td>
<td>20.3 (17.7–23.2)</td>
<td>1.0</td>
<td>7.5 (6.5–8.7)</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>14.1 (10.0–19.3)</td>
<td>1.2</td>
<td>15.9 (8.4–27.1)</td>
<td>0.8</td>
<td>13.3 (8.7–19.5)</td>
</tr>
<tr>
<td>Doxepin</td>
<td>36.3 (33.4–39.3)</td>
<td>3.2</td>
<td>70.5 (62.9–78.8)</td>
<td>3.5</td>
<td>23.3 (20.6–26.2)</td>
</tr>
<tr>
<td>Doxepin</td>
<td>28.1 (17.6–42.6)</td>
<td>2.5</td>
<td>60.1 (32.0–102.7)</td>
<td>3.0</td>
<td>15.9 (7.3–20.1)</td>
</tr>
<tr>
<td>Doxepin</td>
<td>12.4 (8.1–18.4)</td>
<td>1.1</td>
<td>17.0 (8.5–30.4)</td>
<td>0.8</td>
<td>10.2 (5.6–17.2)</td>
</tr>
<tr>
<td>Imipramine</td>
<td>9.9 (3.2–23.2)</td>
<td>0.9</td>
<td>0</td>
<td>–</td>
<td>13.3 (4.3–31.0)</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>15.0 (8.0–25.6)</td>
<td>1.3</td>
<td>35.1 (15.2–69.2)</td>
<td>1.7</td>
<td>7.8 (2.5–18.1)</td>
</tr>
<tr>
<td>Tramipramine</td>
<td>18.8 (17.7–20.0)</td>
<td>1.7</td>
<td>33.7 (31.0–36.5)</td>
<td>1.7</td>
<td>12.6 (11.6–13.8)</td>
</tr>
<tr>
<td>TCAs</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>SNRI: venlafaxine</td>
<td>5.3 (4.2–6.6)</td>
<td>0.46</td>
<td>8.7 (6.4–1.6)</td>
<td>0.43</td>
<td>3.5 (2.5–4.9)</td>
</tr>
<tr>
<td>NaSSA: mirtazapine</td>
<td>3.6 (2.1–5.7)</td>
<td>0.32</td>
<td>4.1 (1.8–8.1)</td>
<td>0.20</td>
<td>3.3 (1.6–6.0)</td>
</tr>
<tr>
<td>SSRIs</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Citalopram</td>
<td>1.7 (1.3–2.3)</td>
<td>0.15</td>
<td>3.3 (2.2–4.7)</td>
<td>0.16</td>
<td>1.0 (0.6–1.6)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>0.5 (0.3–0.9)</td>
<td>0.05</td>
<td>0.6 (0.2–1.3)</td>
<td>0.03</td>
<td>0.5 (0.3–1.0)</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>0.5 (0.2–0.9)</td>
<td>0.04</td>
<td>1.1 (0.4–2.2)</td>
<td>0.05</td>
<td>0.2 (0.05–0.6)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>0.7 (0.3–1.3)</td>
<td>0.06</td>
<td>1.1 (0.3–2.7)</td>
<td>0.05</td>
<td>0.5 (0.1–1.2)</td>
</tr>
<tr>
<td>All five SSRIs</td>
<td>0.9 (0.7–1.1)</td>
<td>0.08</td>
<td>1.6 (1.2–2.1)</td>
<td>0.08</td>
<td>0.6 (0.4–0.8)</td>
</tr>
</tbody>
</table>

TCAs, tricyclic antidepressants; SNRI, serotonin and norepinephrine reuptake inhibitor; NaSSA, noradrenergic and specific serotoninergic antidepressant; SSRIs, selective serotonin reuptake inhibitors.

a: Index of toxicity relative to amitriptyline.
Ketamine

- Widely used in anaesthesia
- Misused
- NMDA receptor antagonist
- Sub-therapeutic doses
- 6 treatment protocols of iv 0.5mg/kg (3 Rx) then 0.75mg/kg
- Emergent evidence base for treatment resistant depression
- Nasal administration currently being trialled.
- Side effects: dry mouth, tachycardia, hypertension, restlessness, visual disturbance, dissociation (usually short lived)
Fig. 2. Global ketamine’s efficacy on depressive symptomatology in non-ECT and ECT studies. All depression assessments were made 24 h after administration in non-ECT studies.
Single infusion (Murrough et al 2015)
Ionescu et al 2016 J Clin Psych

- Open label study
- Intravenous ketamine
- 14 patients
- MDD with suicidal thoughts
Mechanism

• Appears to alter a number of domains associated with suicidality
  • Anxiety
  • Anhedonia
  • Rumination – resting state DMN network data from healthy controls (DMN disruption associated with rumination)
Minor tranquilisers

- Epidemiological studies: increased risk of suicide
  - Poorly controlled for
    - Depression
    - Other psychiatric disorders associated with insomnia
- Suicides associated with single agent hypnotic overdoses

BUT

Insomnia is associated with suicidality
ECT

• No randomised evidence
• Expert consensus supports
• Limited role
  • Cost
  • Availability
  • Associated stigma
  • Involved process
Pharmacotherapy in borderline PD

- Flupenthixol (Montgomery & Montgomery 1982)
  - Reduction in self harm
  - Never replicated

- Paroxetine (Verkes 1998)
  - No difference in repetition of self-harm
  - In those with fewer than 5 past episode more effective

- Fluoxetine (Coccaro 1997)
  - May reduce aggression
Other possible compounds

Tiny doses of opioid could be first fast anti-suicide drug

- Double blind placebo controlled trial
- Suicidal patients (N=40)
- No hx of substance misuse
- Sublingual administration
- 0.1 mg daily for 4 weeks
- In addition to current treatments
- Significant decrease in suicidal ideation

Yovel 2016 AJP

New scientist Feb 2016
Conclusion

- Good medication concordance is protective
- Lithium consistent protective effect
  - Largely limited to bipolar disorder
  - Side effect profile
- Relationship between antidepressants and suicidality remains contested
- Clozapine
- Ketamine
  - Promising findings
  - Duration of treatment effect unknown
  - May provide us with a tool to explore underlying biological mechanisms
  - IV administration limits use currently
- Buprenorphine
QUESTIONS