Outcomes of Long Term Medications

Thomas J Raedler, MD
Email: thomas.raedler@albertahealthservices.ca
Disclaimer

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- Amgen
- AstraZeneca
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- Boehringer-Ingelheim
- Eli Lilly
- Forum (EnVivo)
- Janssen
- Lundbeck
- Novartis
- Otsuka
- Pfizer
- Purdue
- Roche
- Sanofi Aventis
- Sunovion
- Valeant
Questions

• Are medications effective for psychiatric disorders?
• Do all patients with psychiatric disorders benefit from medications?
• Can all psychiatric disorders be treated with medications?
• Have pharmacological interventions changed the long-term course of psychiatric disorders?
Psychotropic agents
pre 1950

- Opium
- Bromides
- Barbiturates
- Hyoscine
- Paraldehyde
- Benzedrine
- Amphetamine
- Thyroxine
Non-pharmacological treatment of psychosis pre 1950

- Physical restraints
- Hydrotherapy
- Insulin coma therapy
- Chemical and electrical shock treatment
- Lobotomy / Leucotomy
- Focus sanitation (‘Eliminate the perils of pus infection’) (dental extraction, colectomy, hysterectomy)
Lithium

Alkali metal

John Cade
"I believe the brain, like any other organ, can get sick and it can also heal."

Mogens Schou
Introduction of chlorpromazine

- Reserpine as the first antipsychotic
  Cave depression and suicide

- Chlorpromazine as an antihistamine used in anesthesia with unexpected psychiatric properties

- 1952 first use in schizophrenia by Jean Delay and Pierre Deniker in Paris

- Additional phenothiazines and butyrophenones synthesized in the 50ies
Other psychotropic agents

Iproniazid
- Originally developed as a tuberculostaticum
- Antidepressant (MAOI) effects discovered in 1952

Chlordiazepoxide
- First benzodiazepine introduced in 1960
Fig. 1. The growth of psychiatric medications.

Antidepressant Use in United States (Million Users)

Source: Behavioral Health, United States, 2012
SAMHSA (Substance abuse and Mental Health Services Administration)
Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses

94 meta-analyses (48 drugs in 20 medical diseases, 16 drugs in 8 psychiatric disorders)

Psychiatric drugs were not generally less efficacious than other drugs

Leucht S et al. BJP 2012;200:97-106
Gap in Levels of Outcome: A Challenge?

- **Response**: Percentage decrease in symptoms

- **Remission (APA consensus)**: SAPS-SANS global rating 2 or less or PANSS item ratings of 3 or less

- **Recovery**: Independent functioning (work, school, social relationships, independent living); requiring minimal or no support (societal perspective) and, personal sense of well being (personal perspective)

Figure 1 Summary of pooled results
Data are n/N (%) unless otherwise stated. The random effects model by DerSimonian and Laird<ce:cross-ref refid="bib17"> 17 </ce:cross-ref> was used throughout, with weights calculated by the Mantel-Haenszel method. NNT...

<table>
<thead>
<tr>
<th>Number of studies included</th>
<th>Drug group</th>
<th>Control group</th>
<th>Mean study duration* (months)</th>
<th>Risk ratio (95% CI)</th>
<th>Absolute difference (95% CI)</th>
<th>NNTB/H (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse 7–12 months</td>
<td>24</td>
<td>392/1465 (27%)</td>
<td>773/1204 (64%)</td>
<td>0.40 (0.33 to 0.49)</td>
<td>-0.39 (-0.46 to -0.32)</td>
<td>3 (2 to 3)</td>
</tr>
<tr>
<td>Relapse independent of duration</td>
<td>62</td>
<td>744/3395 (22%)</td>
<td>1718/2997 (57%)</td>
<td>0.35 (0.29 to 0.41)</td>
<td>-0.38 (-0.43 to -0.33)</td>
<td>3 (2 to 3)</td>
</tr>
<tr>
<td>Participants readmitted to hospital</td>
<td>16</td>
<td>112/1132 (10%)</td>
<td>245/958 (26%)</td>
<td>0.38 (0.27 to 0.55)</td>
<td>-0.19 (-0.27 to -0.11)</td>
<td>5 (4 to 9)</td>
</tr>
<tr>
<td>Dropout for any reason</td>
<td>57</td>
<td>802/2642 (30%)</td>
<td>1130/2076 (54%)</td>
<td>0.53 (0.46 to 0.61)</td>
<td>-0.24 (-0.30 to -0.17)</td>
<td>4 (3 to 6)</td>
</tr>
<tr>
<td>Dropout because of inefficacy</td>
<td>45</td>
<td>412/2539 (16%)</td>
<td>830/2007 (41%)</td>
<td>0.37 (0.31 to 0.44)</td>
<td>-0.27 (-0.34 to -0.19)</td>
<td>4 (3 to 5)</td>
</tr>
<tr>
<td>Participants unimproved/worse</td>
<td>14</td>
<td>614/880 (70%)</td>
<td>569/644 (88%)</td>
<td>0.73 (0.64 to 0.84)</td>
<td>-0.25 (0.35 to 0.14)</td>
<td>4 (3 to 5)</td>
</tr>
<tr>
<td>Violent/aggressive behaviour</td>
<td>5</td>
<td>9/403 (2%)</td>
<td>34/277 (12%)</td>
<td>0.27 (0.15 to 0.52)</td>
<td>-0.09 (-0.37 to 0.01)</td>
<td>11 (5 to 100)</td>
</tr>
<tr>
<td>Participants employed</td>
<td>2</td>
<td>63/130 (48%)</td>
<td>65/129 (50%)</td>
<td>0.96 (0.75 to 1.23)</td>
<td>-0.02 (-0.14 to 0.10)</td>
<td>50 (47 to 810)</td>
</tr>
<tr>
<td>Death (any)</td>
<td>14</td>
<td>5/1240 (&lt;1%)</td>
<td>7/1116 (1%)</td>
<td>0.77 (0.28 to 2.11)</td>
<td>0.00 (-0.01 to 0.00)</td>
<td>∞</td>
</tr>
<tr>
<td>Suicide</td>
<td>8</td>
<td>0/1021</td>
<td>2/920 (&lt;1%)</td>
<td>0.34 (0.04 to 0.58)</td>
<td>0.00 (-0.01 to 0.00)</td>
<td>∞</td>
</tr>
<tr>
<td>Death from natural causes</td>
<td>14</td>
<td>5/1272 (1%)</td>
<td>3/1129 (&lt;1%)</td>
<td>1.24 (0.39 to 3.97)</td>
<td>0.00 (0.00 to 0.01)</td>
<td>∞</td>
</tr>
<tr>
<td>Dropout because of AE</td>
<td>43</td>
<td>129/2437 (5%)</td>
<td>78/1896 (4%)</td>
<td>1.15 (0.70 to 1.91)</td>
<td>0.00 (0.01 to 0.02)</td>
<td>∞</td>
</tr>
<tr>
<td>At least one AE</td>
<td>10</td>
<td>575/1188 (48%)</td>
<td>450/996 (45%)</td>
<td>1.01 (0.87 to 1.18)</td>
<td>0.01 (-0.06 to 0.08)</td>
<td>100 (H17 to 813)</td>
</tr>
<tr>
<td>At least one MD</td>
<td>22</td>
<td>304/1901 (15%)</td>
<td>134/1510 (9%)</td>
<td>1.55 (1.25 to 1.93)</td>
<td>0.06 (0.03 to 0.10)</td>
<td>17 (10 to 33)</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>13</td>
<td>18/1051 (2%)</td>
<td>37/769 (5%)</td>
<td>0.52 (0.28 to 0.97)</td>
<td>-0.02 (-0.02 to 0.01)</td>
<td>100 (H50 to 8100)</td>
</tr>
<tr>
<td>Use of antiparkinsonian medication</td>
<td>7</td>
<td>182/458 (24%)</td>
<td>90/569 (16%)</td>
<td>1.40 (1.03 to 1.89)</td>
<td>0.09 (0.02 to 0.16)</td>
<td>11 (5 to 50)</td>
</tr>
<tr>
<td>Sedation</td>
<td>10</td>
<td>158/1174 (13%)</td>
<td>85/972 (9%)</td>
<td>1.50 (1.22 to 1.84)</td>
<td>0.05 (0.00 to 0.10)</td>
<td>20 (5 to 50)</td>
</tr>
<tr>
<td>Weight gain</td>
<td>10</td>
<td>128/1231 (10%)</td>
<td>61/1090 (6%)</td>
<td>2.07 (2.31 to 2.5)</td>
<td>0.05 (0.03 to 0.07)</td>
<td>20 (14 to 33)</td>
</tr>
</tbody>
</table>

Figure 1 Summary of pooled results Data are n/N (%) unless otherwise stated. The random effects model by DerSimonian and Laird<ce:cross-ref refid="bib17"> 17 </ce:cross-ref> was used throughout, with weights calculated by the Mantel-Haenszel method. NNT...

Stefan Leucht, Magdolna Tardy, Katja Komossa, Stephan Heres, Werner Kissling, Georgia Salanti, John M Davis

**Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis**


http://dx.doi.org/10.1016/S0140-6736(12)60239-6
Figure 3 Forest plot for efficacy of antipsychotics drugs compared with placebo. Treatments are ranked according to their surface under the cumulative ranking (SUCRA) values (<ce:cross-ref id="cecref10" refid="sec1"> appendix p 98</ce:cross-ref>). SMD=sta...

Stefan Leucht, Andrea Cipriani, Loukia Spineli, Dimitris Mavridis, Deniz Örey, Franziska Richter, Myrto Sam...

Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

The Lancet, Volume 382, Issue 9896, 2013, 951 - 962

http://dx.doi.org/10.1016/S0140-6736(13)60733-3
Relationship of Standardized Mean Change to Year of Publication for Patients Receiving Placebo or Low-Dose, Effective Dose, or Intramuscular Medication

The standardized mean change was significantly positively correlated with year of publication for placebo arms (Spearman $r = 0.52$, $n = 39$, $P = .001$) and was significantly negatively correlated with year of publication for the effective dose medication arms (Spearman $r = -0.26$, $n = 208$, $P < .001$), but not for the low-dose medication arms (Spearman $r = 0.32$, $n = 25$, $P = .12$) or the intramuscular medication arms (Spearman $r = -0.14$, $n = 24$, $P = .53$).
Figure Legend:

Proportion of Recent-Onset Schizophrenia Patients Without Psychotic Exacerbation or Relapse as a Function of Medication Adherence or Nonadherence Status (N=49)

Data are based on whether the participant had a period of moderate or greater nonadherence.
Time to Relapse Compared with Placebo

Final analysis results for time to relapse were consistent with the interim analysis (p<0.0001).

The hazard ratio (placebo/paliperidone palmitate) was 3.60 (95% CI: 2.45, 5.28).

The efficacy of paliperidone palmitate with regard to time to relapse was consistent across all subgroups:
- Age
- BMI, sex
- Geographic region

CI, confidence interval; BMI, body mass index
201 pregnant females
History of major depression
Euthymic for three months prior to their last menstrual period
Currently or recently receiving antidepressant medication
Figure 4 Relapse rates after 1 or 2 years' prolongation of antidepressant treatment in patients already treated for 1–2 or 4–6 months after an acute episode of depression

John R Geddes, Stuart M Carney, Christina Davies, Toshiaki A Furukawa, David J Kupfer, Ellen Frank, Guy M G...

Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review
The Lancet, Volume 361, Issue 9358, 2003, 653 - 661
http://dx.doi.org/10.1016/S0140-6736(03)12599-8
Kaplan-Meier Survival Analysis

Time to first relapse after first remission (t6) during 7 years of follow-up in patients assigned to 18 months (547 days) of dose reduction/discontinuation (DR) or maintenance treatment (MT).
From: Recovery in Remitted First-Episode Psychosis at 7 Years of Follow-up of an Early Dose Reduction/Discontinuation or Maintenance Treatment Strategy: Long-term Follow-up of a 2-Year Randomized Clinical Trial


Figure Legend:

Mean Daily Dose in Dose Reduction/Discontinuation (DR) and Maintenance Treatment (MT) During the Last 2 Years of 7-Year Follow-up
Table 2. Recovery, Symptomatic Remission, and Functional Remission After 7 Years of Follow-up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DR (n = 52)</th>
<th>MT (n = 51)</th>
<th>Total Sample (n = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery</td>
<td>21 (40.4)</td>
<td>9 (17.6)</td>
<td>30 (29.1)</td>
</tr>
<tr>
<td>Remission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>36 (69.2)</td>
<td>34 (66.7)</td>
<td>70 (68.0)</td>
</tr>
<tr>
<td>Functional</td>
<td>24 (46.2)</td>
<td>10 (19.6)</td>
<td>34 (33.0)</td>
</tr>
</tbody>
</table>

Table Title:
Recovery, Symptomatic Remission, and Functional Remission After 7 Years of Follow-up

Abbreviations: DR, dose reduction/discontinuation; MT, maintenance treatment.
Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010

Whiteford et al., Lancet 2013; 382: 1575–86

• Mental and Substance Use Disorders:
  183,900,000 DALYs worldwide
  7.4% of all DALYs (5th overall - 5.4% in 1990)
  0.5% YLL (years of life lost to premature mortality)
  22.9% YLD (years lived with disability) - highest

• Depressive Disorders 40.9% of DALYs

• Burden of mental and substance use disorders increased by 37.6% between 1990 and 2010

• Acute schizophrenia highest disability weight of all disorders
More Sobering Facts

• Sustained recovery in less than 14% after a first psychotic episode
• Less than 20% of subjects with schizophrenia are employed in Europe
• Almost 20% of subjects with schizophrenia become homeless during a 1 year follow-up period

Insel, Nature, 2010
Long term outcome in first episode psychosis

• Data from EPPIC in Melbourne, Australia
• Subjects with first episode psychosis
• Median duration of follow-up 7.5 years
• A quarter of subjects had symptomatic remission and social / vocational recovery
• 16.5% had no psychotic relapse

Short duration of untreated psychosis and rapid response to antipsychotics as predictors

Henry 2010; Alvarez-Jimenez 2011
• Poor functional outcomes were not entirely dependent on the development of psychosis. Nonconverters at clinical high risk had poor social outcome (40.3%) and role outcome (45.5%).
• 77 nonconverters, 15 converters
• 35.9% good social and role outcome
  32.6% poor social and role outcome
  47.8% poor social outcome
  48.9% poor role outcome
Questions

• Are medications effective for psychiatric disorders?
• Do all patients with psychiatric disorders benefit from medications?
• Can all psychiatric disorders be treated with medications?
• Have pharmacological interventions changed the long-term course of psychiatric disorders?
Unmet Needs

• Schizophrenia - Negative symptoms
• Schizophrenia – Cognitive dysfunction
• Treatment-refractory mood disorders and anxiety disorders
• Autism
• Eating Disorders
• Substance-use disorders
• Dementia
Thank you for your attention