Psychopharmacology and violent offending

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Disclosures and Conflicts of Interest

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- Consultant to Lundbeck, Organon, Janssen-Cilag, Eli Lilly and Company, and Bristol-Myers Squibb, and has received fees for giving expert opinions to Bristol-Myers Squibb and GlaxoSmithKline, and lecture fees from Janssen-Cilag, Bristol-Myers Squibb, Eli Lilly and Company, Pfizer, Lundbeck, GlaxoSmithKline, AstraZeneca and Novartis.

- A member of Janssen-Cilag Advisory Board since June 2006, a member of Lilly Advisory Board since October 2006, and has research collaboration with Organon since 2007.
What to do...

...and what not to do
<table>
<thead>
<tr>
<th>Psychotropics</th>
<th>Violence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• antipsychotics</td>
<td>• homicides</td>
</tr>
<tr>
<td>• antidepressants</td>
<td>• assaults</td>
</tr>
<tr>
<td>• mood stabilizers</td>
<td></td>
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<tr>
<td>• benzodiazepines</td>
<td></td>
</tr>
<tr>
<td>• medication for addictive disorders</td>
<td></td>
</tr>
</tbody>
</table>
Question: Is primary prevention possible?

- Epidemiology:
  - majority of prisoners in Western society have APD, but most of subjects with APD will not commit severe violent offences
  - the relative risk of violent offending
    - among patients with psychosis (such as schizophrenia) RR/OR 4–10 (Eronen et al., AGP 1996; Hodgins AGP 1992; Hodgins et al., AGP, 1996; Tiihonen et al., Am J Psychiatry 1997; Brennan et al. AGP 2000)
    - among patients with co-existing substance abuse 17–25 (Eronen et al., Schizophr Bull 1996; Räsänen et al. Schizophr Bull 1998)

ANSWER: Not much, because risk of severe violent offending is too low even among dual diagnosis patients
Question: Is secondary prevention possible?

- Epidemiology:
  - high risk populations: who are recidivistic offenders?
    - in Finland about 70–80% are subjects with APD with early onset substance dependence and 10–20% are schizophrenics
  - the relative risk of violent offending among high risk populations:
    - homicide offenders doing the first year after release from prison (n=1584), risk of committing homicide 253-fold (95% CI 145.8–441.9) vs. general population (Eronen et al., Psychiatr Serv 1996)
    - forensic psychiatric patients during the first year after release from hospital (n=281), risk of committing homicide 294-fold (95% CI 11.2–724.7) vs. general population (Tiihonen et al., Forensic Sci Int 1996)

ANSWER: Yes – but how?
Could elucidation of etiology lead to more or less specific treatment/prevention of habitual violent offending?
Mental Disorders and Crime

A
Epidemiological research on the association between risk factors (e.g. mental disorders) and crime.

B
Brain imaging etc.

C
Pharmacological treatment, sociobehavioral interventions.

- Actions of society (education, housing, gun ownership etc.).
NON-PSYCHOTIC OFFENDERS
The etiological background of APD and psychopathy

- Genes (MAO-A, SERT, 5HT$^2$B etc.) vs. environment
- What can be done:
  - genes vs. prevention/treatment during the next decades or centuries
  - Environment vs. prevention/treatment: already now? (Foster and Jones, AGP Nov 2006)
The etiological background of APD and impulsivity

- Neurotransmitters and metabolism
  - treatment via serotonergic system:
    - **mood stabilizors**
    - compliance, adherence to the treatment
    - **naltrexone, acomprosate, disulfiram** in type 1 alcoholism (but no data from type 2 alcoholism)
BACKGROUND: Individuals with repetitive or impulsive aggression in the absence of other disorders may be diagnosed with intermittent explosive disorder according to DSM-IV, but no such diagnostic category exists in ICD-10. Mood stabilisers are often used off-license for the treatment of aggression associated with a variety of psychiatric conditions, but their efficacy in these and in idiopathic aggression is not known.

AIMS: To summarise and evaluate the evidence for the efficacy of mood stabilisers (anticonvulsants/lithium) in the treatment of impulsive or repetitive aggression in adults.

METHOD: A meta-analysis of randomised controlled trials that compared a mood stabiliser with placebo in adults without intellectual disability, organic brain disorder or psychotic illness, identified as exhibiting repetitive or impulsive aggression.

RESULTS: Ten eligible trials (489 participants) were identified. A pooled analysis showed an overall significant reduction in the frequency/severity of aggressive behaviour (standardised mean difference (SMD) = -1.02, 95% CI -1.54 to -0.50), although heterogeneity was high (I² = 84.7%). When analysed by drug type, significant effects were found in the pooled analysis of three phenytoin trials (SMD = -1.34, 95% CI -2.16 to -0.52), one lithium trial (SMD = -0.81, 95% CI -1.35 to -0.28), and two oxcarbazepine/carbamazepine trials (SMD = -1.20, 95% CI -1.83 to -0.56). However, when the results of only those studies that had a low risk of bias were pooled (347 participants), there was no significant reduction in aggression (SMD = -0.28, 95% CI -0.73 to 0.17, I² = 71.4%).
CONCLUSIONS: There is evidence that mood stabilisers as a group are significantly better than placebo in reducing aggressive behaviour, but not all mood stabilisers appear to share this effect. There is evidence of efficacy for carbamazepine/oxcarbazepine, phenytoin and lithium. Many studies, however, were at risk of bias and so further randomised controlled trials are recommended.
The etiological background of APD and impulsivity

- low glucose metabolism (Virkkunen et al., Arc Gen Psychiatry 1994)
- low non-oxidative glucose metabolism (Virkkunen et al., Psychiatry Res. 2009)
Figure 1. A box-plot of non-oxidative glucose (NOG) metabolism comparing recidivistic offenders who had committed at least one new violent offense (left) with non-recidivistic subjects (middle) and healthy controls (right). The mean NOG value of recidivistic offenders was 1.4 S.D. lower when compared with non-recidivistic offenders and 1.6 S.D. lower when compared with healthy controls (F2,86 = 15.7, p = 0.000002; F2,80 = 11.3, p = 0.00005, age, BMI and S-GGT adjusted ANCOVA).
Figure 2. Receiver operating characteristics (ROC) analysis of non-oxidative glucose metabolism values to predict recidivist violent crimes among the offender population (n = 49). The area under curve is 0.85 (95% CI 0.69–0.93).

Treatments affecting glucose metabolism

- Treatment with zinc etc. (Gesch et al. Br J Psychiatry 2002)
Pharmacological treatment of stimulant abuse

- cocaine dependence: modafinil (Dackis et al., Neuropsychopharmacology 2005)
- vaccines
- cocaine dependence and amphetamine dependence: naltrexone depot injection reduced use by about 50%
Percentage of urine samples negative for various drugs of interest

Amphetamine dependence: methylphenidate (N=53)

Results: Patients allocated to aripiprazole had significantly more amphetamine-positive urine samples than patients in the placebo group (odds ratio=3.77, 95% CI=1.55-9.18), whereas patients who received methylphenidate had significantly fewer amphetamine-positive urine samples than patients who had received placebo (odds ratio=0.46, 95% CI=0.26-0.81).

Conclusions: Methylphenidate is an effective treatment for reducing intravenous drug use in patients with severe amphetamine dependence.
Amphetamine dependence: methylphenidate 54mg/day (N=79)


**Findings** Seventy-nine participants were randomized (40 methylphenidate; 39 placebo); 76 received allocated treatment and 27 completed the trial. ITT analysis (n = 78) showed no statistically significant difference in the percentage of positive urines between the methylphenidate and placebo arms (odds ratio: 0.95, 95% confidence interval: 0.83–1.08). However, there was a significant difference (P < 0.05) between the active and placebo arms in retention, the placebo arm displaying a significantly lower retention from 6 weeks that persisted until the end of the trial.

**Conclusions** The trial failed to replicate earlier findings suggesting that methylphenidate was superior to placebo. The low retention rate confounded the ability to draw firm conclusions about efficacy. The higher retention rate was observed in the methylphenidate arm. Any replication of this work would need to consider alternatives to the rigid clinic attendance criteria, and consider an increased dose.
Amphetamine dependence: methylphenidate up to 180 mg/day (N=54)


**Measurements:** The primary end point was relapse to any drug use measured by urine toxicology. Secondary endpoints included relapse to amphetamine use, change in ADHD symptoms, retention to treatment, and time to relapse. **Findings:** The MPH treated group had significantly higher proportion of drug negative urines compared to the placebo group ($P=0.047$), more amphetamine negative urines ($P=0.019$) and better retention to treatment ($P=0.032$). Compared to the placebo group, the MPH group significantly reduced their ADHD symptoms during the trial ($P=0.002$).

**Conclusions:** MPH treatment reduced the risk for relapse to substance use, and reduced ADHD symptoms.
Amphetamine dependence: mirtazapine 30 mg/day (N=60)


Results: Urine positivity decreased from 67% (20 of 30 participants) to 63% (17 of 27) in the placebo arm and from 73% (22 of 30) to 44% (12 of 27) in the mirtazapine arm. The number needed to treat to achieve a negative weekly urine test result was 3.1.

Conclusions: The addition of mirtazapine to substance use counseling decreased methamphetamine use among active users and was associated with decreases in sexual risk despite low to moderate medication adherence. Trial Registration clinicalTrials.gov Identifier NCT00497081.

**Approach:** A review of randomised controlled trials of pharmacotherapies for methamphetamine- or amphetamine-type stimulants was performed using PubMed and Google Scholar databases. Evidence for efficacy of medications is reported.

**Key findings:** Clinical trials have yielded no broadly effective pharmacotherapy. Promising signals have been observed for methylphenidate, naltrexone, bupropion and mirtazapine in subgroups of patients in reducing stimulant use (e.g. patients with less severe dependence at baseline and men who have sex with men), though none has produced an unambiguous, replicable signal of efficacy.
Naltrexone implant for the treatment of polydrug dependence
Objective

Nowadays, the majority of all drug-addicts are polydrug dependent, and no effective pharmacological treatment is currently available for them. Therefore, we aimed to study the overall real-world effectiveness of naltrexone implant in this patient population.
Treatments for opioid dependence

- Methadone
- Buprenorphine
  - Finland
  - Georgia
  - Mauritius
  - USA?
Method

We studied the effectiveness of a naltrexone implant in the treatment of a co-existing heroin and amphetamine polydrug dependence in a 10-week randomized, double-blind, placebo-controlled trial with 100 heroin and amphetamine dependent patients in out-patient setting. Main outcome measures were retention in the study, proportion of drug-free urine samples and improvement in Clinical Global Impression (CGI). Analyses were by intention to treat.
Prodetoxone: Route and Dosage

PRODETOXONE®, tablets for implantation
1000 mg of naltrexone
**Figure 1.** Flowchart of the study. “Lost to follow-up” refers to subjects who dropped out without any notice, and “Refused to participate” refers to patients who expressed that they wanted to stop participating the study.
Figure 2. Retention in the treatment during the 10-week treatment period. At week 10, the retention was 26/50 (52%) among patients with naltrexone vs. 14/50 (28%) among patients with placebo ($p = 0.01$ for difference). Patients were allowed to continue in the trial despite of missing previous visits. Therefore, the retention rate occasionally increased (at weeks 6 and 9) when patients with missing visits at previous week started to participate the treatment again.
<table>
<thead>
<tr>
<th>Rating</th>
<th>Placebo (N=50)</th>
<th>Naltrexone (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Much improved</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Moderately improved</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Minimally improved</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>No change</td>
<td>24</td>
<td>48</td>
</tr>
</tbody>
</table>

a The proportion of patients with much improvement was substantially greater in the naltrexone arm than in the placebo arm ($\chi^2=19.4$, df=1, p<0.001). The evaluations were done at week 0 and week 10 among those patients who completed the study per protocol, and at week 0 and the last visit among those stopping the study prematurely. If the patient could not be evaluated after week 0, the change was rated as “no change.”
Secondary Outcome Measures

- At week 10, patients in the naltrexone group had significantly more heroin-free urine samples (52% compared with 20%; $X^2=11.1$, df=1, $p<0.001$) and more amphetamine-free urine samples, although the difference fell short of significance (40% compared with 24%; $X^2=2.94$, df=1, $p=0.09$).
The rating of subjective effects of amphetamine was available for 18 patients in the placebo group and 22 patients in the naltrexone group. Fifteen patients in the placebo group (83.3%) and three in the naltrexone group (13.6%) reported full effect for amphetamine use, indicating that naltrexone suppressed the euphoric effect more than did placebo ($p<0.001$, Fisher’s exact test). The mean GAF scores at week 10 were 82.0 for the naltrexone group ($N=20$) and 71.9 for the placebo group ($N=28$) (Mann-Whitney U test=$145.5$, $p=0.004$), indicating a better outcome among patients receiving naltrexone.
Table 3. Adverse effects. No statistically significant differences were observed (all p-values > 0.12, Fisher’s exact test).

<table>
<thead>
<tr>
<th></th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>N of patients</strong></td>
<td>50</td>
</tr>
<tr>
<td>Surgical (implantation)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
</tr>
<tr>
<td>Nervousness</td>
<td>1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
</tr>
<tr>
<td>Irritability, nervousness</td>
<td>2</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total number (% of all patients)</strong></td>
<td>9 (18%)</td>
</tr>
</tbody>
</table>
Results

- At week 10, the retention was 52% (26/50) among patients with naltrexone vs. 28% (14/50) among patients with placebo implant (p = 0.01), and the proportion of drug-free urine samples was 38% (19/50) vs. 16% (8/50) (p = 0.01), respectively. Fifty-six per cent (28/50) of the patients with naltrexone showed much or very much improvement in CGI compared with 14% (7/50) of the patients with placebo (p < 0.001, number needed to treat = 3, 95% CI 2–4).
Conclusions

- Naltrexone implants resulted in higher retention in the treatment, decreased heroin and amphetamine use, and improved the clinical condition of patients, thus providing the first evidence of an effective pharmacological treatment for this type of polydrug dependence.
Naltrexone Implant for the Treatment of Polydrug Dependence: A Randomized Controlled Trial

Jari Tiihonen, M.D., Ph.D.
Evgeny Krupitsky, M.D., Ph.D.
Elena Verbiskaya, Ph.D.
Elena Blokhina, M.D., Ph.D.
Olga Mamontova, M.D.
Jaana Föhr, M.D.
Pekka Tuomola, M.D., Ph.D.
Kimmo Kuoppasalmi, M.D., Ph.D.
Vesa Kiviniemi, Ph.D.
Edwin Zwartau, M.D., Ph.D.

Objective: The majority of drug addicts are polydrug dependent, and no effective pharmacological treatment is currently available for them. The authors studied the overall real-world effectiveness of naltrexone implant in this patient population.

Method: The authors assessed the effectiveness of a naltrexone implant in the treatment of coexisting heroin and amphetamine polydrug dependence in 100 heroin- and amphetamine-dependent outpatients in a 10-week randomized, double-blind, placebo-controlled trial. The main outcome measures were retention in the study, proportion of drug-free urine samples, and improvement score on the Clinical Global Impressions Scale (CGI). Analyses were conducted in an intent-to-treat model.

Results: At week 10, the retention rate was 52% for patients who received a naltrexone implant and 28% for those who received a placebo implant; the proportions of drug-free urine samples were 38% and 16%, respectively, for the two groups. On the CGI improvement item, 56% of the patients in the naltrexone group showed much or very much improvement, compared with 14% of those in the placebo group (number needed to treat=3).

Conclusions: Naltrexone implants resulted in higher retention in the study, decreased heroin and amphetamine use, and improved clinical condition for patients, thus providing the first evidence of an effective pharmacological treatment for this type of polydrug dependence.

(Am J Psychiatry 2012; 169:531–536)
Treatment of alcohol dependence


**Aim:** To compare the effects in alcohol-dependent patients of three pharmacotherapies, disulfiram (DIS), naltrexone (NTX), and acamprosate (ACA), when used with a brief manual-based cognitive-behavioural intervention.

**Method:** We conducted a randomized, open label, multicentre naturalistic study in two phases; first, a 12-week continuously supervised medication, followed by targeted medication (TM) up to 52 weeks in addition to a 67-week follow-up period; altogether 119 weeks (2.5 years), in 243 voluntary treatment-seeking alcohol-dependent adult outpatients. Subjects were randomized 1:1:1 to receive supervised NTX, ACA or DIS, 50, 1998, or 200 mg, respectively, per day, plus a brief manual-based cognitive-behavioural intervention. The patients were met in the second and sixth weeks, and then after 3, 6, and 12 months.
Fig. 2. Time to first heavy drink (days) during the continuous medication period (1–12 weeks). Kaplan–Meier survival analysis on the start of heavy drinking. Significant difference between DIS (P = 0.001) and others.


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Fig. 4. Time to first drink (days) during the whole study period (1–52 weeks). Kaplan–Meier survival analysis of the first drink (days) during the whole study period (1–52 weeks). DIS significantly better than NTX and ACA (P = 0.001).
PSYCHOTIC OFFENDERS
The role of structured forensic psychiatric after care

- The forensic approach that includes assessing and managing the risk of violence as well as treating symptoms of schizophrenia led to better outcome than that of general psychiatry (Hodgins et al. Int J For Mental Health 2007)
Recidivistic offending among Finnish forensic schizophrenic patients in 1978–2006
Effects of pharmacological treatments among mentally ill offenders?

**EFFICACY**

- clozapine superior to olanzapine superior to haloperidol among violent inpatients (Krakowski et al., AGP 2006)
Effectiveness vs. efficacy
RCTs  Observational studies

TREATMENT GUIDELINES
Effect size in each study (solid circles) for 10 drugs, with better second-generation antipsychotic efficacy indicated by positive effect sizes

Randomized trials

100 patients

50 not willing to participate the trial

50 willing to participate

40 excluded (co-morbidity, suicidal or antisocial behavior, insufficient compliance, somatic disease)

10 included

5 disappear/quit

5 patients/results
National Hospital Discharge Register

National Prescription Register

National Mortality Register

Results
Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study

Jari Tiihonen, Kristian Wahlbeck, Jouko Lönnqvist, Timo Klaukka, John P A Ioannidis, Jan Volavka, Jari Haukka
Methods

We evaluated a nation-wide cohort of consecutive subjects (n=2230) hospitalized in Finland for the first time due to schizophrenia or schizoaffective disorder between January 1995 and December 2001. National central registers were used to study all-cause discontinuation rates, re-hospitalization rates, and mortality associated with monotherapy with the 10 most frequently used antipsychotic medications. Effectiveness estimates were adjusted with multivariate models and propensity score methods.
Relative risk (RR) of re-hospitalization obtained by using medication as time dependent variable

<table>
<thead>
<tr>
<th>Medication</th>
<th>Number of relapses</th>
<th>PersonIncidence years</th>
<th>Crude RR (95% CI)</th>
<th>Propensity Score + Multivariate Adjusted* RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perphenazine depot</td>
<td>53</td>
<td>187</td>
<td>0.28</td>
<td>0.41 (0.29 to 0.59)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>0.32 (0.22 to 0.49)</strong></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>329</td>
<td>822</td>
<td>0.40</td>
<td>0.59 (0.45 to 0.75)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>0.54 (0.41 to 0.71)</strong></td>
</tr>
<tr>
<td>Clozapine</td>
<td>336</td>
<td>804</td>
<td>0.42</td>
<td>0.61 (0.47 to 0.79)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>0.64 (0.48 to 0.85)</strong></td>
</tr>
<tr>
<td>Chlorprothixene</td>
<td>79</td>
<td>146</td>
<td>0.54</td>
<td>0.79 (0.58 to 1.09)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>0.64 (0.45 to 0.91)</strong></td>
</tr>
<tr>
<td>Thioridazine</td>
<td>115</td>
<td>201</td>
<td>0.57</td>
<td>0.84 (0.63 to 1.12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>0.70 (0.51 to 0.96)</strong></td>
</tr>
<tr>
<td>Perphenazine oral</td>
<td>155</td>
<td>327</td>
<td>0.47</td>
<td>0.69 (0.58 to 0.82)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.85 (0.63 to 1.13)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>343</td>
<td>651</td>
<td>0.53</td>
<td>0.77 (0.60 to 0.99)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.89 (0.69 to 1.16)</td>
</tr>
<tr>
<td>Mixed or rare</td>
<td>775</td>
<td>1229</td>
<td>0.63</td>
<td>0.92 (0.73 to 1.17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.00 (0.78 to 1.28)</td>
</tr>
<tr>
<td>Haloperidol oral</td>
<td>73</td>
<td>107</td>
<td>0.68</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>82</td>
<td>127</td>
<td>0.64</td>
<td>0.94 (0.69 to 1.29)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.06 (0.76 to 1.47)</td>
</tr>
<tr>
<td>Levomepromazine</td>
<td>52</td>
<td>63</td>
<td>0.82</td>
<td>1.21 (0.84 to 1.73)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.09 (0.76 to 1.57)</td>
</tr>
<tr>
<td>No medication</td>
<td>2248</td>
<td>3362</td>
<td>0.67</td>
<td>0.98 (0.77 to 1.23)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.16 (0.91 to 1.47)</td>
</tr>
</tbody>
</table>

* by Poisson regression and by including gender, calendar year, age at the onset of follow-up, the number of previous relapses, and the length of the first hospitalization and follow-up period in the model.
Conclusions

The first and second generation antipsychotics are highly heterogeneous groups in regard to their effectiveness in a real-world setting. Patients treated with perphenazine depot, clozapine or olanzapine have a substantially lower risk for re-hospitalization, or all-cause discontinuation of their initial treatment than patients treated with haloperidol. Excess mortality is seen mostly in those patients who are not using any antipsychotic medication.
A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia
Effectiveness of antipsychotics in first-episode schizophrenia

Objective: Data on the effectiveness of antipsychotics in the early phase of schizophrenia are limited. We examined the risk of rehospitalization and drug discontinuation in a nationwide cohort of 2,588 consecutive patients hospitalized for the first time with a diagnosis of schizophrenia between 2000 and 2007 in Finland.

Method: We linked national databases of hospitalization, mortality, and antipsychotic prescriptions and computed hazard ratios, adjusting for the effects of sociodemographic and clinical variables, the temporal sequence of the antipsychotics used, and the choice of the initial antipsychotic for each patient.
The hazard ratios are adjusted by using age at diagnosis, sex, length of first hospital episode, current and previous use of anxiolytics, hypnotics and sedatives, antidepressants, drugs used in addictive disorders, analgesics, anti-parkinsonian drugs, blood glucose lowering drugs, and lipid modifying agents as co-variates. Concerning risk of rehospitalisation, also the previous use of antipsychotics during the follow-up and the choice of initial antipsychotic (serving as a surrogate for patient’s clinical status at baseline and thus reflecting the clinical correlates determining the selection of treatment) for each patient is adjusted.
FIGURE 1. Risk of Rehospitalisation after the index Hospital Episode by Antipsychotic Treatment Patterns.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n*</th>
<th>Person years</th>
<th>Crude relative risk (95% CI)</th>
<th>Fully adjusted hazard ratio (95% CI) *</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol LAI</td>
<td>1</td>
<td>18</td>
<td>0.29 (0.04–2.05)</td>
<td>0.21 (0.03–1.60)</td>
<td>0.13</td>
</tr>
<tr>
<td>Clozapine</td>
<td>58</td>
<td>412</td>
<td>0.72 (0.53–0.99)</td>
<td>0.48 (0.31–0.76)</td>
<td>0.001</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>134</td>
<td>904</td>
<td>0.76 (0.59–0.98)</td>
<td>0.54 (0.40–0.73)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Other antipsychotics</td>
<td>10</td>
<td>82</td>
<td>0.63 (0.33–1.20)</td>
<td>0.56 (0.29–1.10)</td>
<td>0.09</td>
</tr>
<tr>
<td>Risperidone LAI</td>
<td>15</td>
<td>119</td>
<td>0.65 (0.38–1.11)</td>
<td>0.57 (0.30–1.08)</td>
<td>0.09</td>
</tr>
<tr>
<td>Perphenazine LAI</td>
<td>13</td>
<td>109</td>
<td>0.61 (0.34–1.09)</td>
<td>0.59 (0.31–1.12)</td>
<td>0.11</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>80</td>
<td>321</td>
<td>1.28 (0.96–1.71)</td>
<td>0.92 (0.66–1.28)</td>
<td>0.62</td>
</tr>
<tr>
<td>Zuclopenthixol LAI</td>
<td>6</td>
<td>52</td>
<td>0.59 (0.26–1.35)</td>
<td>0.95 (0.37–2.44)</td>
<td>0.92</td>
</tr>
<tr>
<td>Risperidone oral</td>
<td>113</td>
<td>581</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Perphenazine oral</td>
<td>11</td>
<td>63</td>
<td>0.90 (0.48–1.67)</td>
<td>1.11 (0.57–2.18)</td>
<td>0.76</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>54</td>
<td>217</td>
<td>1.28 (0.93–1.77)</td>
<td>1.11 (0.75–1.64)</td>
<td>0.60</td>
</tr>
<tr>
<td>No treatment</td>
<td>993</td>
<td>2318</td>
<td>2.20 (1.81–2.68)</td>
<td>1.63 (1.30–2.04)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Haloperidol oral</td>
<td>5</td>
<td>13</td>
<td>1.98 (0.81–4.84)</td>
<td>1.79 (0.63–5.09)</td>
<td>0.28</td>
</tr>
<tr>
<td>Zuclopenthixol oral</td>
<td>3</td>
<td>12</td>
<td>1.29 (0.41–4.05)</td>
<td>1.93 (0.57–6.58)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

n = number of rehospitalisations. The hazard ratios are adjusted by using age at diagnosis, sex, length of first hospital episode, the previous use of antipsychotics during the follow-up, current and previous use of anxiolytics, hypnotics and sedatives, antidepressants, drugs used in addictive disorders, analgesics, anti-parkinsonian drugs, blood glucose lowering drugs, and lipid modifying agents as co-variates. The fully adjusted hazard ratios * (shown in the plot) are adjusted by using also the choice of the initial antipsychotic for each patient as a co-variate (reflecting the clinical correlates determining the selection of treatment). The Bonferroni corrected p-value corresponding to the 0.05 statistical significance with 13 multiple comparisons is 0.05/13 = 0.0038.
FIGURE 2. Risk of All-Cause Discontinuation of Initial Antipsychotic Treatment Started within 30 days of Discharge after the Index Hospital Episode.

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>N*</th>
<th>Person years</th>
<th>Crude relative risk (95% CI)</th>
<th>Adjusted hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol LAI</td>
<td>6</td>
<td>6</td>
<td>0.26 (0.11–0.63)</td>
<td>0.39 (0.16–0.97)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>389</td>
<td>313</td>
<td>0.34 (0.30–0.40)</td>
<td>0.39 (0.34–0.46)</td>
</tr>
<tr>
<td>Clozapine</td>
<td>188</td>
<td>196</td>
<td>0.26 (0.21–0.31)</td>
<td>0.43 (0.35–0.54)</td>
</tr>
<tr>
<td>Risperidone LAI</td>
<td>51</td>
<td>40</td>
<td>0.32 (0.23–0.44)</td>
<td>0.44 (0.31–0.62)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>80</td>
<td>45</td>
<td>0.53 (0.42–0.68)</td>
<td>0.53 (0.41–0.70)</td>
</tr>
<tr>
<td>Perphenazine LAI</td>
<td>41</td>
<td>16</td>
<td>0.81 (0.59–1.11)</td>
<td>0.76 (0.54–1.07)</td>
</tr>
<tr>
<td>Zuclopenthixol LAI</td>
<td>30</td>
<td>11</td>
<td>0.86 (0.59–1.24)</td>
<td>0.92 (0.61–1.37)</td>
</tr>
<tr>
<td>Risperidone oral</td>
<td>411</td>
<td>127</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Other antipsychotics</td>
<td>43</td>
<td>13</td>
<td>0.97 (0.70–1.34)</td>
<td>1.04 (0.73–1.49)</td>
</tr>
<tr>
<td>Zuclopenthixol oral</td>
<td>6</td>
<td>2</td>
<td>0.95 (0.42–2.12)</td>
<td>1.23 (0.53–2.86)</td>
</tr>
<tr>
<td>Haloperidol oral</td>
<td>9</td>
<td>1</td>
<td>2.84 (1.47–5.49)</td>
<td>1.45 (0.67–3.17)</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>220</td>
<td>35</td>
<td>1.90 (1.61–2.24)</td>
<td>1.87 (1.54–2.27)</td>
</tr>
<tr>
<td>Perphenazine oral</td>
<td>33</td>
<td>4</td>
<td>2.60 (1.82–3.71)</td>
<td>2.39 (1.57–3.64)</td>
</tr>
</tbody>
</table>

* N= number of patients. MDD indicates the median daily dose, and the figure in parenthesis indicates the number of patients which the calculation was based on (i.e. those who had at least 3 successive purchased prescriptions). The hazard ratios are adjusted by using age at diagnosis, sex, length of first hospital episode, current and previous use of anxiolytics, hypnotics and sedatives, antidepressants, drugs used in addictive disorders, analgesics, anti-parkinsonian drugs, blood glucose lowering drugs, and lipid modifying agents as co-variates.
Results

- Of 2,588 patients, 1,507 (58.2%) collected a prescription for an antipsychotic during the first 30 days after hospital discharge, and 1,182 (45.7%, 95% confidence interval [CI]=43.7–47.6) continued their initial treatment for 30 days or longer. In a pairwise comparison between depot injections and their equivalent oral formulations, the risk of rehospitalization for patients receiving depot medications was about one-third of that for patients receiving oral medications (adjusted hazard ratio=0.36, 95% CI=0.17–0.75). Compared with oral risperidone, clozapine (adjusted hazard ratio=0.48, 95% CI=0.31–0.76) and olanzapine (adjusted hazard ratio=0.54, 95% CI=0.40–0.73) were each associated with a significantly lower rehospitalization risk. Use of any antipsychotic compared with no antipsychotic was associated with lower mortality (adjusted hazard ratio=0.45, 95% CI=0.31–0.67).
Conclusions

- In Finland, only a minority of patients adhere to their initial antipsychotic during the first 60 days after discharge from their first hospitalization for schizophrenia. Use of depot antipsychotics was associated with a significantly lower risk of rehospitalization than use of oral formulations of the same compounds. Among oral antipsychotics, clozapine and olanzapine were associated with more favorable outcomes. Use of any antipsychotic was associated with lower mortality.
Statement

- If there is a depot formulation available, use depot instead of equivalent oral!
- Is there any reasonable argument against switch from oral to depot?
A Nationwide Cohort Study of Oral and Depot Antipsychotics After First Hospitalization for Schizophrenia

Jari Tiihonen, M.D., Ph.D.
Jari Haukka, Ph.D.
Mark Taylor, F.R.C.Psych.
Peter M. Haddad, M.D., F.R.C.Psych.
Maxine X. Patel, M.D., M.R.C.Psych.
Pasi Korhonen, Ph.D.
Polypharmacy
**Context**: Polypharmacy is widely used in the treatment of schizophrenia, although it is believed to have major adverse effects on the well-being of patients. However, it is not known if use of benzodiazepines, antidepressants, or multiple concomitant antipsychotics is associated with increased mortality.
Objective, Design, Setting, Patients, and Main Outcome Measures: We linked national databases of mortality and medication prescriptions in a complete nationwide cohort of 2,588 patients hospitalized in Finland for the first time with a diagnosis of schizophrenia between 2000 and 2007 to compute hazard ratios (HR) for all-cause mortality during antipsychotic, antidepressant and benzodiazepine use in outpatient care, while adjusting for the effects of socio-demographic and clinical variables, geographical location, and both past and current pharmacological treatments.
**Results:** Concomitant use of 2 or more antipsychotics was not associated with increased mortality when compared with antipsychotic monotherapy (HR 0.86, 95%CI 0.51–1.44). Use of antidepressants was also not associated with a higher risk of death (HR 0.57; 0.28–1.16), and it was associated with markedly decreased suicide mortality (HR 0.15; 0.03-0.77). However, the use of benzodiazepines was associated with a substantial increase in mortality (HR 1.91, 1.13–3.22), and this was attributable to both suicidal (HR 3.83; 1.45-10.12) and non-suicidal deaths (HR 1.60; 0.86-2.97). 826 of 904 (91%) of patients having used benzodiazepines had prescriptions containing more than 28 defined daily doses, thus violating treatment guidelines.
**Conclusions:** Benzodiazepine use was associated with markedly increased mortality among patients with schizophrenia, whereas the use of an antidepressant or several concomitant antipsychotics was not. Antidepressant use was associated with decreased suicide mortality. The literature indicates that long-term use of benzodiazepines among patients with schizophrenia is even more prevalent in countries such as US, compared to Finland, which suggests that benzodiazepines may contribute to the excess mortality in this patient population worldwide.
Polypharmacy With Antipsychotics, Antidepressants, or Benzodiazepines and Mortality in Schizophrenia

Jari Tiihonen, MD, PhD; Jaana T. Suokas, MD, PhD; Jaana M. Suvisaari, MD, PhD; Jari Haukka, PhD; Pasi Korhonen, PhD

Arch Gen Psychiatry. 2012;69(5):476-483
Is there anything else we can do?

- Lamotrigine augmentation
- Sarcosine and other glutamatergic drugs
- Treatment of prodromal patients
- Anti-inflammatory analgesics
The efficacy of lamotrigine in clozapine-resistant schizophrenia: A systematic review and meta-analysis

- **Results:** Five trials with 10 to 24 weeks duration and total of 161 randomized clozapine patients were included in the meta-analysis. Lamotrigine was superior to placebo augmentation in both the primary outcome measure (SMD 0.57, 95% CI 0.25–0.89, \( p < 0.001 \); OR 0.19, 95% CI 0.09–0.43, \( p < 0.001 \); NNT 4, 95% CI 3–6) and secondary outcome measures (SMD 0.34, 95% CI 0.02–0.65 for positive symptoms, SMD 0.43, 95% CI 0.11–0.75 for negative symptoms).

- **Conclusions:** This meta-analysis suggests that lamotrigine augmentation may be an effective treatment for patients with clozapine-resistant schizophrenia. A substantial proportion of these most severely ill patients appeared to obtain clinically meaningful benefit from this combination treatment.

What can we do now?

ASPD and SUD

1. individual vs. categorical decision making
   - punishment vs. treatment vs. incapacitation (100 years for second homicide is a fair deal?)
2. obligatory and monitored sobriety
   - disulfiram
   - methylphenidate?
   - naltrexone depot injections?

Psychosis

- structured after-care
- use of clozapine or depot antipsychotic injections
# Prevention of habitual violent offending

## NOW

**Patients with psychosis**
- effective after care
- use of clozapine or depot injections

**Offenders with PD**
- legal power for outpatient care
- use of SSRI?
- use of lithium?
- use of zinc?

**Offenders with substance abuse**
- legal power for outpatient care
- supervised use of disulfiram
- use of mirtazapine?
- use of methylphenidate?
- use of naltrexone depot injections?

## NEXT DECADE

**New pharmacological treatments?** (Such as glycine transporter inhibitors?)

**New pharmacological treatments?**

**New pharmacological treatments?**
- use of methylphenidate, mirtazapine or naltrexone depot injection?
- amfetamine and cocaine vaccines?

## NEXT CENTURY

CURE?
What to do?

1. Use of antipsychotics: Clozapine or LAI
2. Treatment of dependence: disulfiram, long-acting naltrexone
3. Antidepressants are OK
4. Do not use benzos longer than 4 weeks
THANK YOU!