Treatment effects on criminality, violence, drug abuse, accidents and other high risk outcomes

Professor Ian C K Wong
i.wong@ucl.ac.uk or wongick@hku.hk
UCL School of Pharmacy London
and
University of Hong Kong

“A cheerful heart is good medicine, but a crushed spirit dries up the bones. (Proverbs 17:22)”. 
Declaration of interests

• Funding from EU Commission to study safety of methylphenidate
  • ADDUCE (Attention deficit/hyperactivity disorder drugs use chronic effects) Consortium

• Member of NICE ADHD Guideline Development Group

• Funding received from Janssen-Cilag: Prostate cancer treatment (unrelated to the current talk).
Acknowledgement

• ADDUCE (Attention deficit/hyperactivity disorder drugs use chronic effects) Consortium
• Kenneth Man
Outline

• Injury-related medical encounters.
• Suicidal behaviour.
• Adverse psychiatric outcomes: Results from ADDUCE project
  • Evidence mapping from systematic review
• Criminality
• Some broad conclusions
ADHD

• A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with development

• Symptoms presenting in two or more settings (e.g. at home, school, or work), and negatively impacts directly on social, academic or occupational functioning”.

• The symptoms must be present before age 12 [Diagnostic and Statistical Manual of Mental Disorders V (DSM V)]
Three symptom domains

• inattentiveness
• hyperactivity
• impulsivity
Outline

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Hypothesis

• All three factors predispose patients to injuries due to accidents
• Drug treatment reduce the symptoms and theoretically can reduce the accidents and reduce injuries.
Hypothesis

• Clinical trials are not long enough to address this question.

• Research question:
  • Does methylphenidate (MPH) reduce the risk of trauma in children with ADHD?

• Objective:
  • To investigate the association between the use of MPH and trauma related Accident & Emergency (A&E) hospital admission
Methylphenidate and the Risk of Trauma

Kenneth K.C. Man, MPH*, Esther W. Chan, PhD*, David Coghill, MD*, Ian Douglas, PhD*, Patrick Ip, MBBS, MPH*
Ling-pong Leung, MBBS*, Matthew S.H. Tsui, MBBS*, Wilfred H.S. Wong, MMedSc*, Ian C.K. Wong, PhD*

abstract

BACKGROUND AND OBJECTIVE: Children and adolescents with attention-deficit/hyperactivity disorder (ADHD) are prone to sustaining trauma that requires emergency department (ED) admission. Methylphenidate (MPH) can reduce ADHD symptoms and may thus theoretically reduce the risk of trauma-related ED admission, but previous studies do not make this association clear. This study examines this association.

METHODS: A total of 17,381 patients aged 6 to 19 years who received MPH prescriptions were identified by using the Clinical Data Analysis & Reporting System (2001–2013). Using a self-controlled case series study design, the relative incidence of trauma-related ED admissions was compared with periods of patient exposure and nonexposure to MPH.

RESULTS: Among 17,381 patients prescribed MPH, 4,934 had at least 1 trauma-related ED admission. The rate of trauma-related ED admission was lower during exposed periods compared with nonexposed periods (incidence rate ratio [IRR]: 0.91 [95% confidence interval (CI): 0.86-0.97]). The findings were similar only when the incident trauma episode was assessed (IRR: 0.89 [95% CI: 0.82-0.96]). A similar protective association was found in both genders. In validation analysis using nontrauma-related ED admissions as a negative control outcome, no statistically significant association was found (IRR: 0.99 [95% CI: 0.95-1.02]). All sensitivity analyses demonstrated consistent results.

CONCLUSIONS: This study supports the hypothesis that MPH is associated with a reduced risk of trauma-related ED admission in children and adolescents. A similar protective association was found in both male and female patients. This protective association should be considered in clinical practice.
Data source

• Clinical Data Analysis and Reporting System (CDARS)
  • Anonymised territory-wide hospital database
• Developed by the Hong Kong Hospital Authority (HA)
• Includes data from all publicly-funded healthcare providers including: hospitals, ambulatory clinics, primary clinics and A&E.
• Covers all Hong Kong residents (over 7 million).
Clinical Data Analysis and Reporting System (CDARS)

• Patient-specific data in CDARS includes:
  • Diagnosis,
  • Information on hospital admissions and discharges
  • Accident and Emergency admission
  • Out-patient visits
  • Prescription and dispensing information
Study design

• Self-controlled case series
  • each patient serves as their own control

• Only include individuals with both exposure and outcome

• Within-individual comparison
  • Time-invariant confounding effect is removed

• Incidence rate ratios (IRR) are derived
  • comparing the rate of events during exposed periods (on medication) with the rate of off-medication periods

\[
IRR = \frac{\text{Incidence Rate in Exposed Period (on - medication)}}{\text{Incidence Rate in Baseline period (off - medication)}}
\]
## Results

<table>
<thead>
<tr>
<th></th>
<th>IRR</th>
<th>LCL</th>
<th>UCL</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trauma related A&amp;E admission (n=4,934)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All episodes</td>
<td>0.91</td>
<td>0.86</td>
<td>0.97</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Male (n=4,309)</td>
<td>0.92</td>
<td>0.86</td>
<td>0.98</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Female (n=625)</td>
<td>0.83</td>
<td>0.68</td>
<td>1.00</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below 16 years old</td>
<td>0.93</td>
<td>0.87</td>
<td>0.99</td>
<td>0.03</td>
</tr>
<tr>
<td>16 years old and above</td>
<td>0.68</td>
<td>0.53</td>
<td>0.86</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>
Negative control – non-trauma injury related A&E admission

• Negative control
  • IRR = 0.99 (95% CI 0.95 – 1.02), p=0.44
• MPH use is significantly associated with a lower rate of A&E admission due to trauma related injury but not non-trauma related injury.
  • It supports our hypothesis
• Interestingly, older age group has larger effect.
Are our results generalisable?
Effects on medication on medical encounters due to injuries - overall

Man et al CNS Drugs (accepted)
Effects on medication on medical encounters due to injuries with age stratification

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Rate Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Rate Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.1.1 Children and adolescents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dalsgaard 2015</td>
<td>-0.1965</td>
<td>0.0531</td>
<td>19.1%</td>
<td>0.82 [0.74, 0.91]</td>
<td></td>
</tr>
<tr>
<td>Man 2015</td>
<td>-0.0943</td>
<td>0.0288</td>
<td>19.7%</td>
<td>0.91 [0.86, 0.96]</td>
<td></td>
</tr>
<tr>
<td>Mikolajczyk 2015</td>
<td>-0.1393</td>
<td>0.0826</td>
<td>17.9%</td>
<td>0.87 [0.74, 1.02]</td>
<td></td>
</tr>
<tr>
<td>Raman 2013</td>
<td>-0.3857</td>
<td>0.1569</td>
<td>14.1%</td>
<td>0.68 [0.50, 0.92]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>70.9% 0.86 [0.79, 0.93]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\text{Tau}^2 = 0.00$; $\text{Chi}^2 = 5.84$, df = 3 ($P = 0.12$); $I^2 = 49$

Test for overall effect: $Z = 3.54$ ($P = 0.0004$)

| 7.1.2 Adults            |                |     |        |                          |                               |
| Chang 2014              | -0.4589        | 0.2585 | 9.4%   | 0.63 [0.38, 1.05]        |                               |
| Chang 2017              | -0.5158        | 0.0263 | 19.8%  | 0.60 [0.57, 0.63]        |                               |
| Subtotal (95% CI)       |                |     |        | 29.1% 0.60 [0.57, 0.63]  |                               |

Heterogeneity: $\text{Tau}^2 = 0.00$; $\text{Chi}^2 = 0.05$, df = 1 ($P = 0.83$); $I^2 = 0$

Test for overall effect: $Z = 19.69$ ($P < 0.00001$)

Total (95% CI)          | 100.0%         | 0.76 [0.61, 0.93] | 0.61 [0.46, 0.81] |

Heterogeneity: $\text{Tau}^2 = 0.06$; $\text{Chi}^2 = 128.42$, df = 5 ($P < 0.00001$); $I^2 = 96$

Test for overall effect: $Z = 2.59$ ($P = 0.010$)

Test for subgroup differences: $\text{Chi}^2 = 50.70$, df = 1 ($P < 0.00001$), $I^2 = 98.0$

Man et al CNS Drugs (accepted)
Summary of effects of medication on medical encounters due to injuries or trauma

• Current available data support the hypothesis that ADHD treatments is associated with a lower risk of injury-related admission in children, adolescents and adults.
  • Approximately 13% lower.

• This outcome has important clinical and public health implications as well as resource utilisation.

• Injury prevention should be considered in the broader clinical assessment of ADHD medication risks and benefits aside from the traditional consideration of improving symptoms.
Outline

• Injury related medical encounters.
• Suicidal behaviour.
• Adverse psychiatric outcomes: Results from ADDUCE project
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• Some broad conclusions
Stressor-Diathesis model of suicide

ADHD increases impulsivity which can increase risk of suicide-related events.
Hypothesis

• MPH increases dopamine & noradrenaline in the brain
  • Increases the executive function of the frontal lobes.
  • Reduces in impulsivity and aggressiveness.
  • Theoretically MPH should reduce suicidal behaviour.
Association of Risk of Suicide Attempts With Methylphenidate Treatment

Kenneth K. C. Man, MPH; David Coghill, MD; Esther W. Chan, PhD; Wallis C. Y. Lau, BSc; Chris Hollis, PhD; Elizabeth Liddell, PhD; Tobias Banaschewski, MD; Suzanne McCarthy, PhD; Antje Neubert, PhD; Kapil Sayal, PhD; Patrick Ip, MBBS; Martijn J. Schuemie, PhD; Miriam C. J. M. Sturkenboom, PhD; Edmund Sonuga-Barke, PhD; Jan Buitelaar, MD; Sara Carucci, MD; Alessandro Zuddas, MD; Hanna Kovshoff, PhD; Peter Garas, MD; Peter Nagy, MD; Sarah K. Inglis, PhD; Kerstin Konrad, PhD; Alexander Häge, MD; Eric Rosenthal, MD; Ian C. K. Wong, PhD

**IMPORTANCE** Patients with attention-deficit/hyperactivity disorder (ADHD) are at an increased risk of attempting suicide. Stimulants, such as methylphenidate hydrochloride, are the most common treatment for ADHD, but the association between their therapeutic use and suicide is unclear.

**OBJECTIVE** To investigate the association between methylphenidate and the risk of suicide attempts.
Results

Peak before the treatment
Another study

• Chen et al identified an increased risk of suicidal behavior in patients receiving ADHD medications (hazard ratio [HR], 1.31; 95% CI, 1.19-1.44) compared with non-treated patients with ADHD.

• Among stimulant users, a reduced within-patient rate of suicide-related events was seen during treatment periods (HR, 0.81; 95% CI, 0.70-0.94).
  • Chen et al assumed the risk of suicidal behaviour to be constant in non-treatment periods.
  • Our study has shown the assumption is not necessarily true so it is unclear whether stimulants can reduce the suicidal behaviour.
Use of stimulants and suicidal behaviour

• No evidence that stimulants increase the risk of suicidal behaviour.
• Jury is still out there whether stimulants can reduce such behaviour.
Outline

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Adverse psychiatric outcomes of ADHD medication use

• ADDUCE (Attention deficit/hyperactivity disorder drugs use chronic effects) Consortium

• Systematic literature review by ADDUCE consortium
  • Mood disturbance or symptoms of depression
  • Suicide, thoughts of suicide (suicidal ideation), or self-harming behaviour
  • Substance Abuse Disorder (including alcohol and smoking)
  • Psychosis or psychosis-like experiences
  • Tics and dyskinesias
Evidence Mapping – systematic review

Search terms included:
- ADHD
- Methylphenidate
- Psychiatric side effects:
  - Tourette
  - Tics
  - Self-injury
  - Mood Disorders
  - Psychoses
  - Substance use

Inclusion criteria:
- Original article
- Humans
- ADHD population
- Neuropsychiatric harms of MPH
- MPH treatment duration ≥ 12 months

Ovid MEDLINE(R) 1946 to March Week 2 2017 177 Citation(s)

Embase 1980 to 2017 Week 12 5258 Citation(s)

PsycINFO 1806 to March Week 2 2017 1412 Citation(s)

References from Review articles 318 Citation(s)

6660 Non-Duplicate Citations Screened

Inclusion/Exclusion Criteria Applied

6010 Articles Excluded After Title/Abstract Screen

650 Articles Retrieved

Inclusion/Exclusion Criteria Applied

559 Articles Excluded After Full Text Screen

22 Articles Excluded During Data Extraction

69 Articles Included
Study types

All included studies

Comparative Studies: comparators
Non-comparative studies: authors’ subjective judgment

- Huge variety of study designs
- Much of the evidence inconclusive
- Conclusions from comparative studies generally in the direction of either favouring MPH over comparator, or “proceed with caution”
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Criminality and medication use

• ADHD has been associated with criminality and externalizing disorders.
• Beneficial short-term effects of ADHD medication on symptoms of ADHD and associated conduct problems have been shown in some randomized, controlled studies involving children and adults.
Ginsberg et al 2015

• Adult male prisoners with ADHD who completed a 5-week randomized, double-blind, placebo-controlled trial followed by a 47-week open-label extension of osmotic-release oral system methylphenidate in a Swedish high-security prison from 2007 to 2010

• 25 trial completers were prospectively followed up clinically
  • 1 year (24/25, 96% participated fully or in part)
  • 3 years (20/25, 80% participation) after trial
  • Measured ADHD symptoms (observer and self-reports), psychosocial functioning, substance misuse, and criminal reoffending.
Results

- After 3 years, 75% (15/20) of the respondents had been released from prison, and 67% of these (10/15) had employment, usually full time.
- Non-medicated respondents at the 3-year follow-up (5/20) reported more ADHD symptoms, functional impairment, and substance misuse compared with currently medicated respondents (15/20).
- Further, 40% of the respondents self-reported reoffending, indicating a substantially lower relapse rate than expected (70%–80%).
Lichtenstein et al 2012

• Using Swedish national registers, Lichtenstein et al gathered information on 25,656 patients with a diagnosis of ADHD, their pharmacologic treatment, and subsequent criminal convictions in Sweden from 2006 through 2009.

• They used stratified Cox regression analyses to compare the rate of criminality while the patients were receiving ADHD medication, as compared with the rate for the same patients while not receiving medication.
Criminality rate for any crime 2006-2009 during treatment periods vs non-treatment periods among Swedish Patient with ADHD

<table>
<thead>
<tr>
<th>Sex</th>
<th>Number of patients</th>
<th>Number of crimes</th>
<th>Criminality rate ratio</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cox Regression</td>
<td>Stratified Cox Regression*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hazard ratio</td>
<td>95 % Confidence interval</td>
<td>Hazard ratio</td>
<td>95 % Confidence interval</td>
</tr>
<tr>
<td>Males</td>
<td>16,087</td>
<td>23,693</td>
<td>0.70</td>
<td>0.66-0.75</td>
<td>0.68</td>
<td>0.63-0.73</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>9,569</td>
<td>4,112</td>
<td>0.78</td>
<td>0.68-0.90</td>
<td>0.59</td>
<td>0.50-0.70</td>
<td></td>
</tr>
</tbody>
</table>
Interpretation – More considerate people

• Among patients with ADHD, rates of criminality were lower during periods when they were receiving ADHD medication. These findings raise the possibility that the use of medication reduces the risk of criminality among patients with ADHD.

• It may be explained by “Less impulsivity and think twice and less crime”
Alternative interpretations – Smarter Criminal

• Lichtenstein et al. associated the use of medication in patients with ADHD with a reduction in “criminality.” Their definition of criminality is, of necessity, limited to interactions with law enforcement or the criminal-justice system. Because a favorable effect of stimulants on attention has been amply shown, it seems plausible that stimulants may function as performance-enhancing drugs in patients with ADHD who have criminal intent; the medications may affect the will or capacity to plan or commit a crime and successfully evade law enforcement. (David Cohen)
Alternative interpretations – Smarter Criminal
Outline

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Some broad conclusions

• Strong evidence from ADHD pharmacological observational studies
  • Medications reduce injury and trauma related medical encounters
  • Medications does not increase the risk of suicidal behaviour

• Some evidence from ADHD pharmacological observational studies
  • Medications reduce incidence of being arrested for crimes or self-reported crimes.

• Insufficient evidence from ADHD pharmacological observational studies to draw firm conclusions but medications are unlikely to significantly increase the risk of
  • substance misuse
  • Psychiatric and neurological adverse events
Key references


thank you!