Hydrochlorothiazide and risk of skin cancer

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Conflicts of interest

I have participated in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Servier, Novo Nordisk and LEO Pharma, all with funds paid to the institution where I am employed (no personal fees) and with no relation to the work presented today.

LEO Pharma is the manufacturer of a drug containing bendroflumethiazide (Centyl®).

The work is funded by the Danish Council of Independent Research (grant 4004-00234B) and the Danish Cancer Society (grant R72-A4417)
Hydrochlorothiazide, there and back again…
But… you used those data already?
Ehm… Causality you say?
Hypnotics' association with mortality or cancer: a matched cohort study

Daniel F Kripke,¹ Robert D Langer,² Lawrence E Kline¹

ABSTRACT

Objectives: An estimated 6%—10% of US adults took a hypnotic drug for poor sleep in 2010. This study extends previous reports associating hypnotics with excess mortality.

Setting: A large integrated health system in the USA.

Design: Longitudinal electronic medical records were extracted for a one-to-two matched cohort survival analysis.

Subjects: Subjects (mean age 54 years) were 10,529 patients who received hypnotic prescriptions and 23,676 matched controls with no hypnotic prescriptions, followed for an average of 2.5 years between January 2002 and January 2007.

Main outcome measures: Data were adjusted for age, gender, smoking, body mass index, ethnicity, marital status, alcohol use and prior cancer. Hazard ratios (HRs) for death were computed from Cox proportional hazards models controlled for risk factors and using up to 116 strata, which exactly matched cases and controls by 12 classes of comorbidity.
Use of benzodiazepines or benzodiazepine related drugs and the risk of cancer: a population-based case-control study

Anton Pottegård,¹ Søren Friis,² Morten Andersen³ & Jesper Hallas¹

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

• The association between benzodiazepines and benzodiazepine related drugs (BZRD) and cancer risk is disputed.
• A recent cohort study has shown a 35% excess cancer risk among users of hypnotics, including benzodiazepines.

AIM

Studies of the carcinogenic potential of benzodiazepines and related drugs (BZRD) have been equivocal. A recent study reported a 35% excess cancer risk among users of hypnotics, including benzodiazepines.

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Keywords
benzodiazepines, cancer, case-control study, pharmacoepidemiology, population based

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Increased risk of solid renal tumors in lithium-treated patients

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Cystic kidney diseases and toxic interstitial nephritis may be complicated by renal tumors. Long-term lithium intake is associated with tubulointerstitial nephritis and renal cysts but to date such an association with tumors has not been determined. We evaluated this in a retrospective study to determine whether lithium-treated patients were at higher risk of renal tumors compared with lithium-free patients with chronic kidney disease (CKD), and to the general population. Over a 16-year period, 14 of 170 lithium-treated patients had renal tumors, including seven malignant and seven benign tumors. The mean duration of lithium exposure at diagnosis was 21.4 years. The renal cancers included three clear-cell and two papillary renal cell carcinomas, one hybrid tumor with chromophobe and oncocyteoma characteristics, and one clear-cell carcinoma with leiomyomatous stroma. The benign tumors included one renal oncocytoma, one renal papillary carcinoma, and one renal oncocytoma with papillary renal cell carcinoma.

Bipolar disorder is a frequent and severe mood disorder.1 Over the years, lithium has been increasingly recognized as an effective and valuable agent for its treatment and prevention of relapses.1 Although new drugs have recently been developed, lithium is still recommended as a first-line therapy for mood disorders.1 Renal side effects of this treatment, partly due to the narrow therapeutic index of the drug, have given rise to significant concern.2 Indeed, long-term lithium intake may alter the concentrating ability of the kidney, and up to 40% of patients present with polyuria.2 Although serum lithium concentrations are maintained within the therapeutic range, the glomerular filtration rate (GFR) may decline progressively in ~20% of patients, potentially resulting in chronic kidney disease (CKD).3-7 In these cases, renal histopathological findings include tubular atrophy and interstitial fibrosis, which are more commonly seen in CIN than in NCKD.
Long-Term Lithium Use and Risk of Renal and Upper Urinary Tract Cancers

Anton Pottegård,* Jesper Hallas,* Boye L. Jensen,† Kirsten Madsen,‡‡ and Søren Friis§

*Clinical Pharmacology, Institute of Public Health, University of Southern Denmark, Odense, Denmark; †Department of Cardiovascular and Renal Research, University of Southern Denmark, Odense, Denmark; ‡Department of Pathology, Odense University Hospital, Odense, Denmark; §Danish Cancer Society Research Center, Danish Cancer Society, Copenhagen, Denmark

ABSTRACT

Lithium induces proliferation in the epithelium of renal collecting ducts. A recent small-scale cohort study reported a strong association between use of lithium and increased risk of renal neoplasia. We therefore conducted a large-scale pharmacoepidemiologic study of the association between long-term use of lithium and risk of upper urinary tract cancer, including renal cell cancer and cancers of the renal pelvis or ureter. We identified all histologically verified upper urinary tract cancer cases in Denmark between 2000 and 2012 from the Danish Cancer Registry. A total of 6477 cases were matched by age and sex to 259,080 cancer-free controls. Data on lithium use from 1995 to 2012 were obtained from the Danish Prescription Registry. We estimated the association between long-term use of lithium (≥5 years) and risk of upper urinary tract cancer using conditional logistic regression with adjustment for potential confounders. Long-term use of lithium was observed among 0.22% of cases and 0.17% of controls. This yielded an overall relative risk of 1.19 (95% CI: 1.05–1.34).
Original Investigation

Sildenafil Use and Increased Risk of Incident Melanoma in US Men
A Prospective Cohort Study

Wen-Qing Li, PhD; Abrar A. Qureshi, MD, MPH; Kathleen C. Robinson, PhD; Jiali Han, PhD

**IMPORTANCE** The RAS/RAF/mitogen-activated protein kinase and extracellular signal-regulated kinase (ERK) kinase/ERK cascade plays a crucial role in melanoma cell proliferation and survival. Sildenafil citrate (Viagra) is a phosphodiesterase (PDE) 5A inhibitor commonly used for erectile dysfunction. Recent studies have shown that BRAF activation down-regulates PDE5A levels, and low PDE5A expression by BRAF activation or sildenafil use increases the invasiveness of melanoma cells, which raises the possible adverse effect of sildenafil use on melanoma risk.

**OBJECTIVE** To evaluate the association between sildenafil use and risk of incident melanoma among men in the United States.

**DESIGN, SETTING, AND PARTICIPANTS** Our study is a prospective cohort study. In 2000, participants in the Health Professionals’ Follow-up Study were questioned regarding sildenafil use for erectile dysfunction. Participants who reported cancers at baseline were excluded. A total of 25,848 men remained in the analysis.

Invited Commentary

Supplemental content at jamainternalmedicine.com
Use of sildenafil or other phosphodiesterase inhibitors and risk of melanoma

Anton Pottegård*,1, Sigrún Alba Johannesson Schmidt2, Anne Braae Olesen3, Ninah Achacoso4, Stephen K Van Den Eeden4,5, Jesper Hallas1, Henrik Toft Sørensen2, Søren Friis6 and Laurel A Habel4

1Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark; 2Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; 3Department of Dermato-Venerology, Aarhus University Hospital, Aarhus, Denmark; 4Division of Research, Kaiser Permanente Northern California, Oakland, CA, USA; 5Department of Urology, UCSF, San Francisco, CA, USA and 6Danish Cancer Society Research Center, Danish Cancer Society, Copenhagen, Denmark

Background: Phosphodiesterase 5A inhibitors (PDEIs), a common treatment for erectile dysfunction, were recently linked to an increased risk of melanoma.

Methods: We conducted two parallel case–control studies, using the Danish Nationwide Health Registries (DNHR) and the Kaiser Permanente Northern California (KPNC) electronic health records. Identifying men with histologically verified melanoma (cases) matched on birth year to 10 cancer-free controls, we estimated odds ratios (OR) for melanoma associated with high use of PDEIs (≥100 tablets filled), adjusting for available confounders.

Results: We identified 7045 DNHR and 2972 KPNC cases with invasive melanoma. The adjusted OR for invasive melanoma associated with high PDEI use was 1.32 (95% confidence interval (CI) 0.99, 1.49) in DNHR and 0.95 (95% CI 0.78, 1.14) in KPNC.
RACED
Rapid Assessment of Carcinogenic Effects of Drugs
Researchers identify over a thousand drug-cancer associations

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In a new nation- and medication-wide study, the Danish administrative health data

Anton Pottegård
Søren Friis
Rene Defont Christensen
Laurel A. Habel
Joshua J. Gagne
Jesper Hallas
<table>
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<th>Cancer</th>
<th>ATC</th>
<th>Drugname</th>
<th>Cases</th>
<th>Controls</th>
<th>OR</th>
<th>ORAll p</th>
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<tr>
<td>Vulva and vagina (Squamos cell carcinoma)</td>
<td>D07AC01</td>
<td>Betamethasone</td>
<td>21/715</td>
<td>106/7,510</td>
<td>1.84 (1.13-3.00)</td>
<td>1.07 0.01</td>
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<td>Estradiol</td>
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<td>255/1,856</td>
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<td>C09CA03</td>
<td>Valsartan</td>
<td>10/3,197</td>
<td>58/31,971</td>
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<td>Cervix uteri (Squamos cell carcinoma)</td>
<td>G02BB01</td>
<td>Vaginal ring with progesterone</td>
<td>11/3,188</td>
<td>56/31,911</td>
<td>2.03 (1.05-3.90)</td>
<td>0.98 0.01</td>
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<td>Cervix uteri (Squamos cell carcinoma)</td>
<td>L04AX01</td>
<td>Azathioprine</td>
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<td>57/31,973</td>
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<td>1.34 0.08</td>
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<td>Cervix uteri (Adenocarcinoma)</td>
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<td>Fluoxetine</td>
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<td>58/7,123</td>
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<td>Cervix uteri (Other)</td>
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<td>Felodipine</td>
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<td>Glimepiride</td>
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<td>593/50,460</td>
<td>1.87 (1.51-2.33)</td>
<td>0.95 0.09</td>
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<td>Corpus uteri (Adenocarcinoma, endometrioid)</td>
<td>B03BB01</td>
<td>Folic acid</td>
<td>26/5,070</td>
<td>154/50,639</td>
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<td>Corpus uteri (Adenocarcinoma, endometrioid)</td>
<td>C02CA01</td>
<td>Prazosin</td>
<td>16/5,110</td>
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<td>0.98 0.07</td>
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<td>Corpus uteri (Adenocarcinoma, endometrioid)</td>
<td>C03AB01</td>
<td>Bendroflumethiazide and pc</td>
<td>886/3,738</td>
<td>6,961/39,620</td>
<td>1.38 (1.28-1.50)</td>
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<td>C03DA01</td>
<td>Spironolactone</td>
<td>79/5,004</td>
<td>520/50,341</td>
<td>1.57 (1.23-2.00)</td>
<td>1.08 0.07</td>
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<td>Corpus uteri (Adenocarcinoma, endometrioid)</td>
<td>C03DB01</td>
<td>Amiloride</td>
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<td>29/51,252</td>
<td>4.19 (2.14-8.22)</td>
<td>1.09 0.07</td>
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<td>Corpus uteri (Adenocarcinoma, endometrioid)</td>
<td>C03EB01</td>
<td>Furosemide and potassium</td>
<td>11/5,117</td>
<td>45/51,213</td>
<td>2.52 (1.30-4.87)</td>
<td>0.95 0.07</td>
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<td>Corpus uteri (Adenocarcinoma, endometrioid)</td>
<td>C09CA02</td>
<td>Eprosartan</td>
<td>10/5,119</td>
<td>53/51,216</td>
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<td>1.13 0.08</td>
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<td>C09CA04</td>
<td>Ibisesartan</td>
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<td>259/50,881</td>
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<td>Corpus uteri (Adenocarcinoma, endometrioid)</td>
<td>D07XC01</td>
<td>Betamethasone</td>
<td>13/5,068</td>
<td>73/50,777</td>
<td>1.79 (0.99-3.23)</td>
<td>0.97 0.04</td>
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<td>Corpus uteri (Adenocarcinoma, endometrioid)</td>
<td>G03CX01</td>
<td>Tobilone</td>
<td>160/4,935</td>
<td>459/50,613</td>
<td>3.64 (3.03-4.38)</td>
<td>1.28 0.02</td>
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<td>Corpus uteri (Adenocarcinoma, endometrioid)</td>
<td>G03DC02</td>
<td>Noraloxone</td>
<td>37/4,974</td>
<td>207/50,454</td>
<td>1.77 (1.24-2.51)</td>
<td>1.30 0.07</td>
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<td>Corpus uteri (Adenocarcinoma, endometrioid)</td>
<td>G03FB01</td>
<td>Norgestrel and estrogens</td>
<td>65/5,040</td>
<td>312/50,785</td>
<td>2.09 (1.60-2.74)</td>
<td>1.26 0.02</td>
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<td>Corpus uteri (Adenocarcinoma, endometrioid)</td>
<td>M04AA01</td>
<td>Allopurinol</td>
<td>73/5,027</td>
<td>340/50,715</td>
<td>2.19 (1.69-2.83)</td>
<td>1.10 0.02</td>
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<td>N02CC06</td>
<td>Eletroprost</td>
<td>15/5,111</td>
<td>65/51,162</td>
<td>2.33 (1.33-4.08)</td>
<td>0.96 0.05</td>
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<td>S01GX09</td>
<td>Opatatin</td>
<td>12/5,095</td>
<td>73/50,951</td>
<td>1.65 (0.89-3.03)</td>
<td>0.84 0.02</td>
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<td>Corpus uteri (Adenocarcinoma, other)</td>
<td>J01EB02</td>
<td>Sulfaframizole</td>
<td>23/783</td>
<td>142/8,020</td>
<td>1.65 (1.04-2.60)</td>
<td>1.00 0.06</td>
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<tr>
<td>Corpus uteri (Adenocarcinoma, other)</td>
<td>M01A08</td>
<td>Etodolac</td>
<td>16/899</td>
<td>101/8,989</td>
<td>1.62 (0.94-2.79)</td>
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<td>Corpus uteri (Sarcomas)</td>
<td>A10BB12</td>
<td>Glimperide</td>
<td>14/558</td>
<td>73/5,646</td>
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<td>0.95 0.09</td>
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<td>S01EE01</td>
<td>Latanoprost</td>
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<td>0.94 0.07</td>
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<td>A10BA02</td>
<td>Metformin</td>
<td>22/396</td>
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<td>1.52 (0.93-2.48)</td>
<td>0.95 0.10</td>
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<td>Digoxin</td>
<td>14/401</td>
<td>75/4,089</td>
<td>2.01 (1.11-3.65)</td>
<td>1.07 0.04</td>
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<td>D07AC01</td>
<td>Betamethasone</td>
<td>11/489</td>
<td>51/4,975</td>
<td>2.09 (1.08-4.04)</td>
<td>1.07 0.08</td>
</tr>
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</table>

Pottegård et al. EBioMedicine 2016 May; 7:73-9
Hydrochlorothiazide and amiloride
Squamous cell carcinoma of the lip

OR = 6.93
(95%CI, 4.70-10.2)

Pottegård et al. EBioMedicine 2016 May; 7:73-9
Use of hydrochlorothiazide and risk of lip cancer
633 SCC lip cancer cases
63 067 population controls
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<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>Adjusted OR</th>
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<tr>
<td>Non-use</td>
<td>494</td>
<td>55,666</td>
<td>1.0 (ref.)</td>
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<tr>
<td>Ever-use</td>
<td>139</td>
<td>7401</td>
<td>2.1 (1.7–2.6)</td>
</tr>
<tr>
<td>High use (≥25,000 mg)</td>
<td>94</td>
<td>2771</td>
<td>3.9 (3.0–4.9)</td>
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<tr>
<td><strong>Cumulative amount</strong></td>
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<td></td>
</tr>
<tr>
<td>1–4999 mg</td>
<td>16</td>
<td>1745</td>
<td>1.0 (0.6–1.7)</td>
</tr>
<tr>
<td>5000–9999 mg</td>
<td>12</td>
<td>1083</td>
<td>1.2 (0.7–2.2)</td>
</tr>
<tr>
<td>10,000–24,999 mg</td>
<td>17</td>
<td>1802</td>
<td>1.1 (0.7–1.7)</td>
</tr>
<tr>
<td>25,000–49,999 mg</td>
<td>20</td>
<td>1253</td>
<td>1.8 (1.2–2.9)</td>
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<tr>
<td>50,000–74,999 mg</td>
<td>12</td>
<td>460</td>
<td>2.9 (1.6–5.3)</td>
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<tr>
<td>75,000–99,999 mg</td>
<td>8</td>
<td>254</td>
<td>3.4 (1.7–7.0)</td>
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<tr>
<td>≥100,000 mg</td>
<td>54</td>
<td>804</td>
<td>7.7 (5.7–10.5)</td>
</tr>
<tr>
<td>Drug Class</td>
<td>Odds ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------------</td>
<td></td>
<td></td>
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<tr>
<td>Hydrochlorothiazide</td>
<td>3.9</td>
<td></td>
<td></td>
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<tr>
<td>Calcium-channel blockers</td>
<td>1.1</td>
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<tr>
<td>ACE-inhibitors</td>
<td>0.9</td>
<td></td>
<td></td>
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<tr>
<td>ATII-antagonists</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bendroflumethiazide</td>
<td>1.2</td>
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Use of hydrochlorothiazide and risk of non-melanoma skin cancer
71,553 BCC cases
1,430,883 population controls

8,629 SCC cases
172,462 population controls
<table>
<thead>
<tr>
<th>Drug</th>
<th>BCC</th>
<th>SCC</th>
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<td>Hydrochlorothiazide</td>
<td>1.30</td>
<td>3.80</td>
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<td>Calcium-channel blockers</td>
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<td>1.00</td>
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<td>ACE-inhibitors</td>
<td>0.99</td>
<td>1.01</td>
</tr>
<tr>
<td>ATII-antagonists</td>
<td>1.08</td>
<td>0.90</td>
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<td>Bendroflumethiazide</td>
<td>1.05</td>
<td>0.96</td>
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<td>Furosemide</td>
<td>0.93</td>
<td>1.23</td>
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Use of hydrochlorothiazide and risk of melanoma
<table>
<thead>
<tr>
<th>Type</th>
<th>Prevalence</th>
<th>Odds Ratio (95% CI)</th>
<th>p&lt;sub&gt;trend&lt;/sub&gt;</th>
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<tr>
<td>Melanoma (all)</td>
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<td>1.22 (1.09-1.36); p&lt;sub&gt;trend&lt;/sub&gt;=0.42</td>
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<tr>
<td>Superficial spreading</td>
<td>72%</td>
<td>1.11 (0.97-1.27); p&lt;sub&gt;trend&lt;/sub&gt;=0.73</td>
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</tr>
<tr>
<td>Nodular</td>
<td>9%</td>
<td>2.05 (1.54-2.72); p&lt;sub&gt;trend&lt;/sub&gt;=0.01</td>
<td></td>
</tr>
<tr>
<td>Lentigo</td>
<td>3%</td>
<td>1.61 (1.03-2.50); p&lt;sub&gt;trend&lt;/sub&gt;=0.16</td>
<td></td>
</tr>
</tbody>
</table>
Use of hydrochlorothiazide and risk of rare skin cancers
### Merkel cell carcinoma (97 cases)

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Users</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-use</td>
<td>77</td>
<td>1,549</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>Ever use</td>
<td>20</td>
<td>308</td>
<td>1.0 (0.6-1.8)</td>
</tr>
<tr>
<td>High use (≥50,000 mg)</td>
<td>11</td>
<td>87</td>
<td>2.3 (1.1-4.8)</td>
</tr>
</tbody>
</table>

**Cumulative amount**

- **1-49,999 mg**: 9 cases, 221 users, OR 0.6 (0.3-1.3)
- **50,000-99,999 mg**: (n<5) cases, 45 users, OR (-)
- **≥ 100,000 mg**: 7 cases, 42 users, OR 3.3 (1.3-8.3)

### Malignant adnexal skin tumour (132 cases)

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Users</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-use</td>
<td>111</td>
<td>2,311</td>
<td>1.0 (ref.)</td>
</tr>
<tr>
<td>Ever use</td>
<td>21</td>
<td>309</td>
<td>1.4 (0.9-2.4)</td>
</tr>
<tr>
<td>High use</td>
<td>13</td>
<td>73</td>
<td>3.6 (1.9-7.0)</td>
</tr>
</tbody>
</table>

**Cumulative amount**

- **1-49,999 mg**: 8 cases, 236 users, OR 0.7 (0.4-1.6)
- **50,000-99,999 mg**: 5 cases, 46 users, OR 2.4 (0.9-6.5)
- **≥ 100,000 mg**: 8 cases, 27 users, OR 5.6 (2.4-13.3)
# Overview of papers

<table>
<thead>
<tr>
<th>Topic</th>
<th>Authors</th>
<th>Journal</th>
<th>Year</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signal (screening)</td>
<td>Pottegård et al.</td>
<td>EBioMedicine 2016 May; 7:73-9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanomer</td>
<td>Pottegård et al.</td>
<td>JAMA Intern Med. 2018 Aug 1;178(8):1120-1122</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PRAC recommendations on signals
Adopted at the 3-6 September 2018 PRAC meeting

This document provides an overview of the recommendations adopted by the Pharmacovigilance Risk Assessment Committee (PRAC) on the signals discussed during the meeting of 3-6 September 2018 (including the signal European Pharmacovigilance Issues Tracking Tool [EPITT]$^2$ reference numbers).

PRAC recommendations to provide supplementary information are directly actionable by the concerned marketing authorisation holders (MAHs). PRAC recommendations for regulatory action (e.g. amendment of the product information) are submitted to the Committee for Medicinal Products for Human Use (CHMP) for endorsement when the signal concerns Centrally Authorised Products (CAPs), and to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh)
Hydrochlorthiazid - Risiko for non-melanom hudkræft (basalcellerkræm, spinocellulært karcinom).

Kære læger og andet sundhedspersonale
Efter aftale med Det Europæiske Lægemiddelagentur og Lægemiddelstyrelsen ønsker indehaverne af markedsføringstilladelser på lægemidler indeholdende hydrochlorthiazid at informere om følgende:

**Resumé**

- Farmakoepidemiologiske studier har vist en øget risiko for non-melanom hudkræft (NMSC) (basalcellerkræm (BCC), spinocellulært karcinom (SCC)) ved eksponering for stigende akkumulerede doser af hydrochlorthiazid (HCTZ).
- Patienter, som tager HCTZ alene eller i kombination med anden medicin, bør informeres om risikoen for NMSC og opfordres til at undersøge huden regelmæssigt for eventuelle nye læsioner samt ændringer af eksisterende, og til at informere lægen om alle mistænkelige hudlæsioner.
- Mistænkelige hudlæsioner bør undersøges, og undersøgelsen bør muligvis inkludere histologiske undersøgelser af biopsier.
- Patienter bør opfordres til at begrænse eksponering for sollys og UV-stråler, og bruge passende solbeskyttelse ved eksponering for sollys og UV-stråler, for at minimere risikoen for hudkræft.
- Det er relevant at genoverveje brugen af HCTZ hos patienter, som tidligere har haft hudkræft.

**Baggrund for sikkerhedsproblemet**

Lægemidler, som indeholder HCTZ, anvendes udbredt til behandling af hypertension, til behandling af hypernatremi og som diuretikum. Hydrochlorthiazid er et diuretikum, der virker ved at forhindre natriumabsorptionen i nieren. Dette fører til en lavere saltindhold i blodet og en fornødnet vandudskuelse. Hydrochlorthiazid kan også have karzinominducerende effekter på hudens epithelceller. Studier har vist, at der er en signifikant øget risiko for hudkræft hos patienter, som tager HCTZ, sammenlignet med patienter, der ikke tager HCTZ. Risikoen øger med tiden og er størst hos patienter, der har haft hudkræft i vejret.
Replication!
Norway
Holland
Australia
Spain
Taiwan
US
Hydrochlorothiazide, there and back again…

But… you used those data already?

Ehm… Causality you say?
Are you reusing data!?
Clarity
Orthogonality
Orthogonal predictions: follow-up questions for suggestive data

Alexander M. Walker
(Pharmacoepidemiol Drug Saf 2010)

Precautions for proactive surveillance

Alexander M. Walker and Robert P. Wise
(Pharmacoepidemiol Drug Saf 2002)

Re-using Mini-Sentinel data following rapid assessments of potential safety signals via modular analytic programs

Toh et al.
(Pharmacoepidemiol Drug Saf 2013)
Reuse of data sources to evaluate drug safety signals: When is it appropriate?

Shirley V. Wang\textsuperscript{1} | Martin Kulldorff\textsuperscript{1} | Robert J. Glynn\textsuperscript{1} | Joshua J. Gagne\textsuperscript{1} | Anton Pottegård\textsuperscript{2} | Kenneth J. Rothman\textsuperscript{3} | Sebastian Schneeweiss\textsuperscript{1} | Alexander M. Walker\textsuperscript{4}

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1 | INTRODUCTION

When can the same data source that generated a safety hypothesis also be used to evaluate it? Regulators who oversee health products frequently turn to health insurance claims, electronic medical records, as well as registries of drugs, devices, and diseases to support their decision making. In addition to protocol-based studies, these sources are often leveraged to conduct exploratory drug safety research. Metanalysis of such published studies has identified that safety signals from randomized controlled trials (RCTs) and observational studies often provide similar estimates of drug effects, but that these estimates can vary due to differences in sample selection and measurement. This can raise concerns about whether the data that were used to identify the initial safety signal will also affect follow-on studies in a similar way. The concern is that data from comparisons made in the initial analysis may drive the results of more comprehensive analyses that make the same comparisons. No one argues for bulking up a new analysis with already-examined data. The warning in the International Society for Pharmacoepidemiology and Outcomes Research and the International Society for Pharmacoepidemiology (ISPOR/ISPE) report's fifth recommendation would be that the data should be presented in a meta-analysis framework.
Some of us were members of a joint task force between the International Society for Pharmacoconomics and Outcomes Research and the International Society for Pharmacoepidemiology.

The warning in the International Society for Pharmacoconomics and Outcomes Research and the International Society for Pharmacoepidemiology (ISPOR/ISPE) report's fifth recommendation was against replicating a potentially biased analysis with a similarly biased study.
Hydrochlorothiazide, there and back again…
But… you used those data already?
Ehm… Causality you say?
Are you claiming causality?
”We are estimating associations in an attempt to estimate causal relationships”
Hill criteria

- Strength
- Consistency
- Specificity
- Temporality
- Biological gradient
- Plausibility
- Coherence
- Experiment
- Analogy
Meeting January 14 1965

President’s Address

observed association to a verdict of causation? Upon what basis should we proceed to do so?

I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of ‘causation’. The ‘cause’ of illness may be immediate and direct, it may be remote and indirect underlying the observed association. But with the aims of occupational, and almost synonymously preventive, medicine in mind the decisive question is whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A. How such a change exerts that influence may call for a great deal of research. However, before deducing ‘causation’ and taking action we shall not invariably have to sit around awaiting the results of that research. The whole chain may have to be unravelled or a few links may suffice. It will depend upon circumstances.

Disregarding then any such problem in semantics we have this situation. Our observations reveal an association between two variables, perfectly clear-cut and beyond what we would care to attribute to the play of chance. What aspects of that association should we especially consider before deciding that the most likely
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