Glucocorticoid use and risk of suicide: a Danish population-based case-control study

Suicide is an important public health problem, with nearly 800,000 people dying worldwide every year. The World Health Organization has declared suicide prevention an international priority[1]. Glucocorticoid treatment is prevalent and beneficial for many chronic diseases[2], but also associated with severe psychiatric adverse effects[3].

Evidence on an association between glucocorticoid treatment and suicide is sparse[4,5]. A study conducted in patients registered at UK general practices[4] pooled suicides and suicide attempts, although acknowledging that they represent two different phenomena that may or not be related. Persons treated with oral glucocorticoids were 7-fold more likely to attempt or die from suicide shortly after initiation of treatment, compared to persons with the same underlying conditions who did not receive these medications. A Canadian case-control study[5], focusing on people aged 66 years or more, found an unadjusted odds ratio of 1.33 (95% CI: 0.88-2.00) for the association of glucocorticoid use and suicide. There is a need to confirm the association between glucocorticoid use and suicide in a large sample representative of the general population, and to evaluate whether the association depends on glucocorticoid administration form, time since initiation of glucocorticoid treatment, and underlying medical conditions and comorbidities.

We examined the association between glucocorticoid use and suicide in a registry-based population-based case-control study in Denmark in the period between January 1, 1995 and December 31, 2015 (cumulated population of 7,559,392 persons). From the Danish Register of Causes of Death[6], we identified 14,028 suicide cases, and from the Civil Registration System[7] we sampled 140,278 population controls using risk-set sampling and matching by birth year and sex. The suicide date served as the index date for cases and controls.

We used the Danish National Prescription Registry, covering all Danish pharmacies[8], to identify all prescriptions for glucocorticoids redeemed by cases and controls before their index date, and defined present, recent and former users of glucocorticoids as individuals who redeemed their most recent glucocorticoid prescription 0 to 90 days, 91 to 365 days, and more than 365 days before the index date, respectively. We further divided present users into new (individuals who redeemed their first-ever prescription ≤90 days before their index date) and prevalent (individuals who redeemed their most recent prescription ≤90 days before their index date and had a prior prescription redemption ever). The cumulative dose of most recent oral glucocorticoid prescription was calculated to assess a dose-response effect based on prednisolone equivalents.

We examined oral glucocorticoids as well as injectable glucocorticoids, inhaled glucocorticoids, and glucocorticoids administered topically in the intestine. For the locally acting glucocorticoids, we considering only exclusive use of each type. As regard covariates, we used the Danish Health Registries[7] to obtain information on treatment indications (obstructive pulmonary disease, rheumatic diseases, renal diseases, inflammatory bowel disease, skin diseases, other autoimmune diseases, and cancer), comorbidities (psychiatric diseases, cardiovascular diseases, diabetes, osteoporosis, alcohol-related disorders), and co-medication use (opioids and antiepileptic medications).

We used logistic regression to estimate crude and adjusted incidence rate ratios (IRRs) for suicide among present, new, prevalent, recent and former users of glucocorticoids compared to never users. As we used risk-set sampling, the estimated odds ratios from the logistic regression provided unbiased estimates of the IRRs[9]. We found that cancer modified the association and therefore stratified our analyses by cancer. We further estimated incidence rate differences using a back-calculation method.

Median age for both cases and controls was 53 years, and 72% were men; 10% of cases and 7.3% of controls had a prior cancer diagnosis, and 67% of cases and 20% of controls had a prior psychiatric disease.

New use of oral glucocorticoids was associated with a 7-fold increased risk of suicide in individuals with cancer (adjusted IRR=7.2, 95% CI: 5.0-11), and with a 2-fold increased risk in individuals with other treatment indications (adjusted IRR=2.0, 95% CI: 1.5-2.8), compared to never use. The rate differences were 7.6 per 10,000 person years (95% CI: –1.7 to 17) and 1.4 per 10,000 person years (95% CI: –8.9 to 12), respectively.

The median cumulative dose of most recent oral glucocorticoid prescription was higher among individuals with cancer than without (2,000 mg vs. 500 mg prednisolone equivalents), and we found a dose-response effect. Adjusted IRRs for suicide according to the prednisolone-equivalent cumulative dose of most recent prescription were 1.2 (95% CI: 0.36-4.0) for dose <250 mg; 3.0 (95% CI: 1.2-7.8) for 250-499 mg; 3.4 (95% CI: 1.9-6.2) for 500-999 mg and 20 (95% CI: 10-41) for doses ≥1000 mg, compared to never use.

The association was consistent across treatment indications and comorbidities, stronger among people below 30 and above 50 years of age, and similar among men and women. Recent and former use of oral glucocorticoids, as well as other administration forms (inhaled, injectable, and topically in the intestine), were not associated with suicide. Other administration forms have lower bioavailability, lower systemic absorption and are often used in lower doses compared to systemic glucocorticoids, which may explain these findings.

We conducted several sensitivity analyses. Residual confounding by disease severity cannot be entirely ruled out. However, our results remained robust to confounding by cancer stage and timing. We calculated E-values to examine the impact of potential unmeasured confounding. The E-value indicated that an unmeasured confounder needed to be associated with both glucocorticoid use and suicide with a relative risk of 14 and 3.4, in cancer and non-cancer patients respectively, to fully explain our findings (i.e., only strong confounding could explain our findings).

We concluded that oral glucocorticoid initiation was associated with suicide in a dose-dependent manner, with findings of a 7-fold increased risk in cancer patients and a 2-fold increased risk in patients treated for other medical conditions. The particularly strong association in individuals with cancer may be explained by high-dose treatment.

Given the widespread use of glucocorticoids, our study deserves clinical and public health attention. Awareness of the association between new use of oral glucocorticoids and suicide may enhance prevention efforts for an extremely serious global public health problem.

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