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Comparative efficacy and safety of carbamazepine in adults without severe mental illness, with aggressive and violent interpersonal behavior: A systematic review and meta-analysis

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ABSTRACT

Background: Violent and aggressive interpersonal behavior is a serious public health concern. Evidence for management approaches of violence in non-psychiatric populations is limited. Although it is widely used as an off-label treatment to manage aggression and impulsivity, there is a lack of systematically collected evidence on the efficacy and safety of carbamazepine for this indication.

Aim: Determine the efficacy and safety of carbamazepine in non-institutionalized adults without severe mental illness, with aggressive and violent interpersonal behavior.

Methods: We systematically searched PubMed, Medline, CINAHL, EMBASE, PsycInfo, CENTRAL, OpenGrey and ClinicalTrials.gov. We included randomized controlled trials assessing the efficacy of carbamazepine in adults without severe mental illness in reducing violent interpersonal behavior, compared to no carbamazepine or other pharmacological treatment modalities. We extracted data from published reports and planned to conduct meta-analyses.

Results: We reviewed 3447 citations, retrieved 17 full-texts and identified 2 eligible studies. Carbamazepine significantly reduced interpersonal aggression among women with borderline personality disorder but not so among men with impulsive aggression. Given the paucity of results, we could not perform a quantitative analysis.

Conclusions: Quality evidence supporting the use of carbamazepine in the management of aggressive interpersonal behavior in adults without severe mental illness is lacking. Further studies are warranted.

1. Introduction

The World Health Organization (WHO) defines violence as "the intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community, that either results in or has a high likelihood of resulting in injury, death, psychological harm, maldevelopment or deprivation" (WHO, 2002). Violence has been traditionally classified as either self-directed, interpersonal or collective (WHO, 2002). Interpersonal violence includes acts of aggression carried out by an individual against family members or members of the community for personal motives (WHO, 2002). However, interpersonal violence is not a homogeneous construct and is classically divided into reactive aggression, defined as "aggressive response to a perceived threat or provocation" and proactive aggression, defined as "planned antisocial behavior that anticipates a reward or dominance over others" (Waltes, Chiocchetti, & Freitag, 2016).

Interpersonal violence is a major public health concern. The global rate of homicide reached 6.7 per 100,000 population in 2012 (WHO, 2014) with intimate partner violence contributing to around 14% of the total (Stockl et al., 2013). The WHO Global Burden of Disease (GBD) project estimated the 2013 age-standardized rates (per 100,000 population) of assault by firearm at 50.0 and assault by sharp object at 107.6 (Collaborators, 2015). Although 80% of homicide victims and 95% of homicide perpetrators are men (UNODC, 2014), women, children and the elderly bear most of the burden associated with non-fatal assault injuries (WHO, 2014).

Interpersonal violence also exerts a huge global economic burden, especially on healthcare systems. In the United States of America (USA),

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the direct and indirect costs of gunshot and cutting and stabbing wounds were estimated to be 177 billion dollars in 1992 (Miller & Cohen, 1997). In 2008, the total cost per-murder was estimated to be close to 9 million dollars in the USA (McCollister, French, & Fang, 2010).

Given the impact on public health and the major economic burden, the research community has been active in evaluating interventions for managing violent urges, focusing mainly on reactive aggression (Rosell & Siever, 2015). There is extensive literature on the management of violent behavior in adults with severe mental illnesses, i.e. psychosis and/or mania (Varshney, Mahapatra, Krishnan, Gupta, & Deb, 2016). However, there is limited evidence regarding the management of aggression in people without severe mental illness. Non-pharmacological interventions such as cognitive behavioral therapy were shown to be ineffective (Jahanfar, Howard, & Medley, 2014; Smedslund, Dalsbo, Steiro, Winsvold, & Clench-Aas, 2007). Some mood stabilizers and antipsychotics were found to be effective in modulating anger in patients with severe personality disorders (Ingenhoven, Lafay, Rinne, Passchier, & Duivenvoorden, 2010). In a Cochrane systematic review published in 2010 (Huband, Ferriter, Nathan, & Jones, 2010), there was no firm evidence regarding the efficacy of mood stabilizers in managing aggression and impulsivity.

Carbamazepine is an antiepileptic drug which was first synthesized in 1953 and was observed to have positive effects on the mood and behaviors of epileptic patients (Scott, 1993). Its multiple mechanisms of action include inhibiting voltage-dependent sodium channels, facilitating GABA activity, and inhibiting catecholamine release (Stoner et al., 2007). While carbamazepine is approved for the treatment of bipolar mania (Lexicomp), there is limited evidence as to its efficacy in managing aggressive behavior in adults without severe mental illness. Recent systematic reviews found carbamazepine to be effective in reducing self-harm in women with borderline personality disorder (Huband et al., 2010) and in reducing impulsive aggression in the forensic population (Felthous, Lake, Rundle, & Stanford, 2013). Although it is widely used as a medication to manage aggression and impulsivity (Felthous & Stanford, 2015; Schatzberg, Cole, & DeBattista, 2015), carbamazepine is not approved to be used for this indication (Lexicomp). An up-to-date systematic review can provide much-needed information about whether there is evidence that supports the use of carbamazepine for this indication.

Our objective was to systematically review the benefits and harms of carbamazepine in adults without severe mental illness and with aggressive and violent interpersonal behavior, compared to no treatment or to other pharmacological treatments. Our primary outcome measure was the reduction in aggressive and violent interpersonal behavior measured using an objective instrument such as a scale. Our secondary outcome measure was the occurrence of any adverse events, including mortality events.

2. Methods

2.1. Eligibility criteria

We included studies meeting the following criteria:

- Population: participants aged 18 years or older;
- Intervention: oral carbamazepine irrespective of the dose, regimen, duration of treatment and drug formulation (immediate vs. extended-release);
- Comparison: either no active comparator (e.g., placebo) or another oral pharmacological treatment modality (e.g., anti-epileptics, antipsychotics);
- Outcomes: aggressive and violent interpersonal behavior with an objective measurement such as a rating scale;
- Study design: randomized-controlled trials.

We excluded studies of incarcerated or hospitalized participants because they are subjected to different environmental conditions than the general population. We also excluded studies with participants diagnosed with severe mental illness, i.e. psychotic disorders or mania. While there is no consensus definition of severe mental illness, psychoses and mania have regularly been included as such and have been extensively studied with regards to violent behavior (Fazel & Grann, 2006; Varshney et al., 2016). Furthermore, we excluded studies with participants diagnosed with neurodegenerative diseases or traumatic brain injury. We did not exclude studies with participants diagnosed with substance use disorders or with personality disorders.

2.2. Search strategy

We searched the following databases up until May 2016: MEDLINE, PubMed, PsycINFO, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, CINAHL and OpenGrey (available in supplementary material). In addition, we searched ClinicalTrials.gov for ongoing relevant trials. We also scanned the reference list of included studies and relevant reviews. We did not restrict our search to language, publication date or publication status. We designed the search strategy with a medical librarian experienced in systematic review searches.

2.3. Study selection

We uploaded the literature search results to a reference management software. Two teams of two reviewers (EG and RK; OG and PN) screened the titles and the abstracts of identified citations independently and in duplicate. We got full texts for citations judged as potentially eligible by at least one of the reviewers. Two teams of two reviewers (EG and RK; OG and PN) then screened the full texts in duplicate and independently. The reviewers compared results and resolved any disagreements through discussion and consensus, or when needed (Lee et al., 2011), through the help of a third reviewer (FT). We documented the reasons for exclusion of full texts using standardized screening forms.

2.4. Data extraction

Two reviewers (EG and OG) extracted data from the full texts of the eligible studies independently and in duplicate. The reviewers resolved disagreements through discussion and consensus. We attempted to contact corresponding authors of eligible studies to inquire about missing information.

For each eligible study, we extracted the following using a standardized form:

- Methods: study design, duration of trial;
- Participants: age, sex, educational level, socioeconomic status, ethnicity, trial setting, eligibility criteria, number randomized and number of completers;
- Intervention: number of treatment arms, dose, formulation, frequency and duration of administration of carbamazepine;
- Comparator: type of comparator, dose, formulation, frequency and duration of administration;
- Outcomes: outcomes assessed, their measurement methods, and length of follow-up;
- Type and source of financial support, conflicts of interest;
- Trial registration.

2.5. Risk of bias assessment

For each included study, we assessed the risk of bias using the Cochrane risk of bias tool ("Table 8.5.a: The Cochrane Collaboration's tool for assessing risk of bias," 2011). The tool addresses the following 6 domains: random sequence generation, allocation concealment,