Journal of Affective Disorders 225 (2018) 221–226

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Can we recommend mirtazapine and bupropion for patients at risk for bleeding?: A systematic review and meta-analysis

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ABSTRACT

Background: Many studies have reported that selective serotonin reuptake inhibitors (SSRI) are associated with an increased risk of bleeding. Mirtazapine and bupropion, which commonly lack serotonin reuptake inhibition, have been recommended as alternatives for patients who are at risk for bleeding. However, the evidence for these recommendations is insufficient.

Methods: We conducted a systematic search, systematic review, and meta-analysis to investigate an evidence-based approach for the bleeding risks of mirtazapine and bupropion. From 1946 to May 2017, a total of 3981 studies were searched from PubMed, Embase, and the Cochrane Library. Among the studies, two independent reviewers selected studies per predefined eligibility criteria.

Results: A total of five meta-analyses were conducted. Patients taking mirtazapine were at a greater risk of gastrointestinal bleeding (OR = 1.17, 95% CI = 1.01–1.38) than those who did not take antidepressants. No differences were observed in the bleeding risk between mirtazapine and SSRI or between bupropion and SSRI.

Limitations: The number of studies included in the meta-analysis was small.

Conclusion: Our results suggest that it is premature to recommend mirtazapine and bupropion for patients who have a bleeding risk. More studies with larger sample sizes and longitudinal follow-ups are warranted.

1. Introduction

For decades, selective serotonin reuptake inhibitors (SSRI) have been used for the treatment of major depressive disorders (MDD) (Schmidt et al., 1988; Tulloch and Johnson, 1992). Given the simple mechanism of action, SSRI were initially considered to have a better safety profile than tricyclic antidepressants (TCA) (Anderson, 2000; Peretti et al., 2000). However, subsequent studies suggested that SSRI are not so 'selective' (Stahl, 1998) and are associated with various types of adverse events (Carvalho et al., 2016; Moret et al., 2009).

One of the consistently reported adverse events is bleeding. Soon after the implementation of SSRI, bleeding events due to fluoxetine (Aranth and Lindberg, 1992), paroxetine (Ottervanger et al., 1994), and sertraline (Calhoun and Calhoun, 1996) were reported. The first case-control study demonstrated that SSRI had higher risk for upper gastrointestinal (GI) bleeding than controls (de Abajo et al., 1999). In that study, the relative risks of SSRI compared to controls were 2.1 (95% *CI* = 0.9–5.1) to 4.3 (95% *CI* = 2.2–8.3). Although some inconsistent findings have suggested a lack of connection between SSRI and bleeding (Barbui et al., 2009), recent meta-analyses have shown that SSRI cause increased upper GI bleeding (Anglin et al., 2014; Jiang et al., 2015) and intracranial hemorrhage (Hackam and Mrkobrada, 2012).

The possible mechanisms by which SSRI increase the bleeding risk is the attenuated coagulative function of serotonin from platelets. Generally, platelet-released serotonin is an agonist for platelet activity (Skop and Brown, 1996). The serotonin receptor on the surface of a platelet acts similarly to those in the neurons in the brain (Lesch et al., 1993). Therefore, SSRI inhibit serotonin reuptake and decrease the availability of serotonin within the platelet, which reduces the coagulative effects of serotonin (Halperin and Reber, 2007; Maurer-Spurej, 2005).

Alternatively, several researchers recommend the use of antidepressants without serotonin transporter reuptake inhibition, particularly mirtazapine and bupropion (Jeong et al., 2014; Sayadipour et al., 2012; Wang et al., 2014; Weinrieb et al., 2003). However, contrary to those recommendations, the safety of bupropion and mirtazapine relative to bleeding risk has not been thoroughly investigated

In this systematic review and meta-analysis, we intended to identify the bleeding risk associated with the use of mirtazapine and bupropion.

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http://dx.doi.org/10.1016/j.jad.2017.08.002
Received 29 May 2017; Received in revised form 15 July 2017; Accepted 3 August 2017
Available online 08 August 2017
0165-0327/

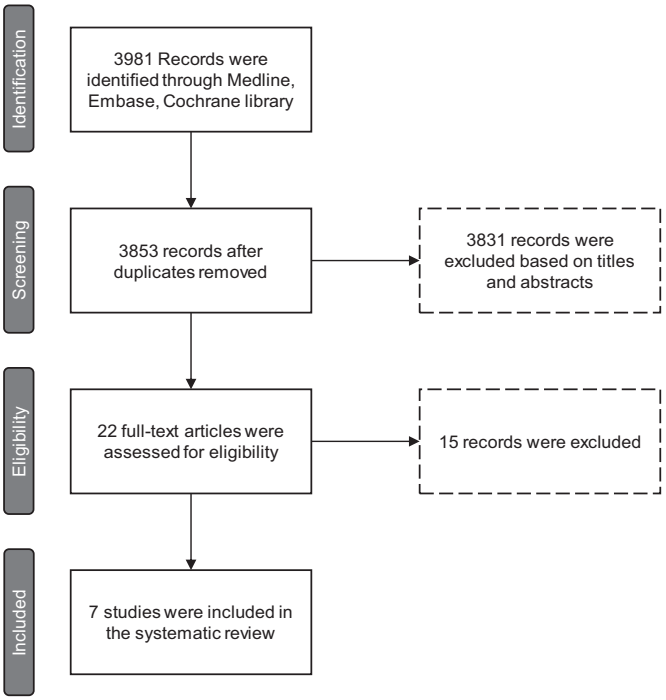

Fig. 1. Flow chart of searches for studies that investigated the risk of bleeding with mirtazapine and bupropion.

2. Methods

For a high standard of conducting and reporting the systematic review and meta-analysis, all of the processes were conducted as suggested by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009) (Fig. 1). We contacted the authors of the published studies for additional information as required.

2.1. Eligibility criteria

We only included studies that reported the bleeding risk of mirtazapine and bupropion compared to controls or SSRI users separately. Studies that calculated the bleeding risk of bupropion and/or mirtazapine combined with other classes of antidepressants were excluded. Case-control and cohort studies that primarily intended to investigate the relationship between bleeding risk and antidepressants were included. The language was restricted to English.

2.2. Information sources and search strategy

One of the investigators (HY) searched the Embase (1966 to present), Pubmed (1946 to present), and Cochrane Library (1998 to present) databases in May 2017. Given the initially searched literatures, two investigators (SE and KS) conducted selection/exclusion procedures independently. Those procedures included a search for secondary references cited in other literatures.

The basic search strategy was [(antidepressants OR selective serotonin reuptake inhibitor OR paroxetine OR fluvoxamine OR sertraline OR fluoxetine OR citalopram OR escitalopram OR reboxetine OR duloxetine OR venlafaxine OR bupropion OR mirtazapine) AND (bleeding OR hemorrhage)].

2.3. Data synthesis and analysis

We used the random effects model to investigate the pooled odds ratio (*OR*) across the studies. If various indices for antidepressants exposure were used, the index that indicated the most recent exposure to antidepressants was used. The adjusted *OR* in each study was primarily used for the meta-analysis. When the adjusted *OR* could not be used, then each number for the exposure to antidepressants and the onset of bleeding events were used.

The risk of bias within the studies was evaluated with the Newcastle–Ottawa Scales (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

To test the degree of heterogeneity of the trials, we used the Q statistic and I^2. Generally, an I^2 of 0% indicates no observed heterogeneity, 25% represents low heterogeneity, 50% represents moderate heterogeneity, and 75% represents high heterogeneity (Higgins et al., 2003). In this study, we considered an I^2 of 50% or higher as a significant heterogeneity result. The statistical threshold for the significance of Q was set at $p < 0.10$. To identify any publication bias, visual inspections with funnel plots and Egger's regression test were conducted. The entire statistical analysis was conducted using Comprehensive Meta-Analysis version 3.0 Software (Biostat, Englewood, NJ, USA).

3. Results

3.1. Study selection

A flow chart using PRISMA is presented in Fig. 1. Through a systematic electronic database search and a manual search in the literature, a total of 3981 studies were obtained. After the duplicates were removed, 3853 studies remained. After screening the titles and abstracts, 3831 studies were excluded because they were not eligible for our meta-analysis. Finally, seven studies were included in our meta-analysis after a thorough review of the full-texts. Among these, six studies were included in the five meta-analyses.

Regarding the studies with mirtazapine, six case-control studies and one cohort study were identified. There were three case-control studies with the bleeding risk of bupropion. Whereas five of six studies with mirtazapine reported GI bleeding, only one of three studies with bupropion separately reported risk of GI bleeding.

3.2. Study characteristics

Table 1 summarizes the characteristics of the 7 studies. We conducted a total of five meta-analyses with the 6 studies for mirtazapine and bupropion, respectively: (1) any types of bleeding risk for mirtazapine compared to SSRI, (2) GI bleeding risk for mirtazapine compared to SSRI, (3) any types of bleeding risk for mirtazapine compared to no-antidepressants, (4) GI bleeding risk for mirtazapine compared to no-antidepressants, and (5) any types of bleeding risk for bupropion compared to SSRI. Meta-analysis for the cohort study with the bleeding risk of mirtazapine and bupropion could not be conducted due to the paucity.

3.3. Case-control studies

The bleeding risk between mirtazapine and SSRI was not significant in terms of any type of bleeding (OR = 1.00, 95% CI = 0.87–1.14) (Supplementary Fig. 1) or in GI bleeding (OR = 1.03, 95% CI = 0.89–1.19) (Fig. 2). Among the five studies for mirtazapine, one study reported the bleeding risk both due to any cause and due to GI-related causes. The pooled estimated OR (1.18 (95% CI = 1.01–1.38)) suggested that mirtazapine was associated with a greater risk for GI bleeding than the no-antidepressants group. (Supplementary Fig. 2) No significant differences were observed in the risk for all types of bleeding with mirtazapine compared to the no-antidepressants group (OR = 1.12, 95% CI = 0.97–1.29) (Supplementary Fig. 3). Bupropion had also no statistical differences in the risk of bleeding from SSRI (Fig. 3).