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REVIEW ARTICLE

Efficacy And Tolerability Of Antidepressants In Palliative Care Patients With Anxiety And Depression – A Systematic Review

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Key Words: Depression, Palliative Care Patients, Antidepressants, Randomized Control Trials With Parallel / Placebo Arms

ABSTRACT

Depression and anxiety, amongst other clinical symptoms, are commonly faced by palliative patients approaching end of life due to terminal life limiting illness. The aim of this study was to systematically review Randomized Controlled Trials on 'Efficacy and Tolerability of Antidepressants in Palliative Patients with Anxiety and Depression' based on set criterion (scores on Hospital Anxiety and Depression Scale - Depression and Anxiety Subscales; HAD-D and HAD-A or other validated scales. A research protocol was first prepared and the PICOS selection process of trials for systematic review employed. A rigorous search was then carried out on Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE (Excerpta Medical Database) and other databases and search engines employing standard search parameters. A total of 7106 study titles were obtained in January 2017. These study titles were then vetted, and 6234 remained after duplicates removed. Only 26 were selected and full articles were obtained electronically by late February 2017. The measurement tools used to assess and monitor clinical improvement during the studies include among others, the Hamilton Rating Scale for Depression (HRSD), Montgomery-Asberg Depression Rating Scale (MADRS), Clinical Global Impression (CGI), Zung Self-Rating Depression Scale (ZSRDS) and the Beck Depression Inventory (BDI). The full text copies of all potentially relevant papers that fulfilled the stage 1 inclusion criteria were obtained and screened for inclusion and exclusion criteria. Subsequently selected studies were screened for methodological quality. All relevant data from these studies were then extracted. The data was then synthesized, findings discussed and conclusions drawn, then a formal dissertation report written out. Analysis across all the included trials shows

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that the heterogeneity was 52 % with all trials analysed simultaneously. But when a subgroup comprising the 7 trials using SSRIs versus Placebo was analysed, heterogeneity reduced to 0%. It can be concluded that in most of the 15 included trials, the Odds Ratio (OR) was more than 1 and the corresponding Absolute Risk Reduction (ARR) was positive and likely represented that the relative risk reduction (or response to the drug) was higher than in the placebo group. The NNT values showed that the response to the interventional drug was satisfactory in most of these trials and this better response was attributable to efficacy of the drug, placebo effect and also due to chance but unlikely due to chance alone. The overall effect of 4.64 too suggests that the null hypothesis could be rejected. A total of 4 studies showed a negative ARR value for their investigational drug versus placebo; and thereby also yielding a Number Needed to Harm (NNH) value which could be explained by low efficacy and / or poor tolerability of the investigational antidepressant. Evidence from this systematic review is in keeping with findings of previous reported systematic reviews on a similar theme. However, it is difficult to make a recommendation in favour of any one antidepressant over another in this subgroup of patients based on efficacy alone. However, it can be concluded that SSRIs such Sertraline and NASSA group drugs were less likely to cause severe side effects compared to tricyclic antidepressants and should be recommended as first line antidepressants in palliative patients if used judiciously.

BACKGROUND

Depression and anxiety, amongst other clinical symptoms, are commonly faced by palliative patients approaching end of life due to terminal life limiting illness. Studies found that at least 17 % were clinically depressed and 20-40% had anxiety as compared to the incidence in the general population of 3% and 9% respectively.

OBJECTIVES AND AIMS

The aim of this study was to systematically review Randomized Controlled Trials on ‘Efficacy and Tolerability of Antidepressants in Palliative Patients With Anxiety and Depression’ based on set criterion (scores on Hospital Anxiety and Depression Scale - Depression and Anxiety Subscales; HAD-D and HAD-A or other validated scales.

METHODOLOGY

A research protocol was first prepared and the PICOS selection process of trials for systematic review employed. A rigorous search was then carried out on Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE (Excerpta Medical Database) and other databases and search engines employing standard search parameters. The full text copies of all potentially relevant papers that fulfilled the stage 1 inclusion criteria were obtained, saved on the Medley application and screened for inclusion and exclusion criteria. Subsequently selected studies were screened for methodological quality. All relevant data from these studies were than extracted and keyed into an Excel database and relevant tables and diagrams created on the Cochrane Review Manager 5 App. The data was then synthesized, findings discussed and conclusions drawn, then a formal dissertation report written out.

Findings

A total of 7106 study titles were obtained in January 2017. These study titles were then vetted, and 6234 remained after duplicates removed. Only 26 were selected and full articles were obtained electronically by late February 2017. Upon scrutinizing the study designs, inclusion and exclusion criteria for the review, only 15 randomized controlled trials were finally selected by mid-April 2017, for data extraction and analysis in this systematic review. The measurement tools used to assess and monitor clinical improvement during the studies include among others, the Hamilton Rating Scale for Depression (HRSD), Montgomery-Asberg Depression Rating Scale (MADRS), Clinical Global Impression (CGI), Zung Self-Rating Depression Scale (ZSRDS) and the Beck Depression Inventory (BDI).

It can be concluded that in most of the 15 included trials, the Odds Ratio (OR) was more than 1 and the corresponding Absolute Risk Reduction (ARR) was positive and likely represented that the relative risk reduction (or response to the drug) was higher than in the placebo group. The Numbers Needed to Treat (NNT) values showed that the response to the interventional drug was satisfactory in most of these trials and this better response was attributable to efficacy of the drug, placebo effect and also to chance but unlikely due to chance alone. This is true for all the included trials where OR was stated except Leentjens A et al 2003 and Wermuth L et al 1998 which showed an OR value below 1 (0.50 and 0.31 in these 2 respective studies). A total of 4 studies showed a negative ARR value for their investigational drug versus placebo; and thereby also yielding a Number Needed to Harm (NNH) value as stated in the table above which could be explained by low efficacy and / or poor tolerability of the investigational antidepressant. These studies include Leentjens et al 2003 (which studied Sertraline versus placebo in patients with Parkinson's Disease), Wermuth L et al 1998 (which studied Atomoxetine versus Placebo in patients with Parkinson's Disease), Menza M et al 2009 (which studied Paroxetine versus Nortriptyline versus Placebo in patients with Parkinson's Disease) and yielded a negative ARR value of 11.7 and a corresponding NNH of 9 for Nortriptyline versus placebo and Musselman D et al 2006 (which studied Paroxetine versus Desipramine versus

Placebo in patients with Breast Cancer) and yielded negative ARR values and corresponding NNH values for both Paroxetine and Nortriptyline versus Placebo. It might be postulated that the drugs used in these trials were poorly tolerated and yielded poor response in this sub-group of patients.

Analysis across all the included trials shows that the heterogeneity was 52 % with all trials analysed simultaneously. But when a subgroup comprising the 7 trials using SSRIs versus Placebo was analysed, heterogeneity reduced to 0%. The NNT values showed that the response to the interventional drug was satisfactory in most of these trials and this better response was attributable to efficacy of the drug, placebo effect and also due to chance but unlikely due to chance alone. The overall effect of 4.64 too suggests that the null hypothesis could be rejected.

Subjects dropped out of trials due to a wide variety of reasons including personal reasons, worsening of primary medical illness, poor tolerability of the interventional drugs, side effects resulting from other concurrent treatment such as radiotherapy or chemotherapy which would ultimately result in poor tolerability of the investigational drug and any other food or drug for that matter due to vomiting and nausea. The dropout rates were fairly high and in the range of 0% to 27.5%. As we were however reporting on studies done on palliative patients, whose disease and prognosis could suddenly change, a high dropout rate is to be expected. This however, could result in attrition bias which could have affected the overall validity of the results of the trial. Some recent studies have excluded the dropouts from the final analysis as in the case of Schiffer R B et al.

CONCLUSION

In conclusion, this study has succeeded in drawing reliable conclusions with a high level 1A of evidence being a systematic review comprising of 15 randomized controlled trials. Evidence from this systematic review is in keeping with findings of previous reported systematic reviews on a similar theme. However, it is difficult to make a recommendation in favour of any one antidepressant over another in this subgroup of patients based on efficacy alone. However, it can be concluded that SSRIs such Sertraline, and NASSA group drugs were less likely to cause severe side effects compared to tricyclic antidepressants and should be recommended as first line antidepressants in palliative patients if used judiciously.

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