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Research report

Moderation of antidepressant and placebo outcomes by baseline severity in late-life depression: A systematic review and meta-analysis

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ABSTRACT

Background: Baseline severity is a crucial moderator of trial outcomes in adult depression, with the advantage of antidepressants over placebo increasing as severity increases. However, this relationship has not been examined in late-life depression.

Methods: PubMed, Embase, Web of Science, PsycINFO, and Cochrane were searched for studies published through September 2014. Randomized, acute phase, and double-blind studies comparing an antidepressant group with a placebo group in depressed elderly patients were included.

Results: Nineteen studies met all inclusion criteria. Within-group effect sizes revealed significant improvement in antidepressant groups ($g=1.35$, $p<.000$), as well as in placebo groups ($g=.96$, $p<.000$). Change in depressive symptoms assessed by Hamilton Depression Rating Scale (HDRS) was moderated by baseline severity in antidepressant groups ($Z=2.67$, $p=.008$) and placebo groups ($Z=4.46$, $p<.000$). However, this would be expected as a result of regression toward the mean, and mean differences between groups did not increase ($r=.19$, $p=.469$) as a function of baseline severity.

Limitations: Limited to published data and information was only analyzed at the level of treatment groups.

Conclusion: Baseline severity was not associated with an antidepressant–placebo difference and placebo responses are large in the treatment of depressed elderly people. We propose a stepwise approach, i.e., to initially offer elderly depressed patients psychosocial interventions and only consider antidepressants if patients do not respond.

1. Introduction

Although the placebo effect and its moderators have been examined extensively in adult populations with major depressive disorder (MDD) (Brunoni et al., 2009; Kirsch et al., 2008), comparable studies for late-life depression are scarce. There is no agreement upon definition of late-life depression; the term may be used to refer to patients with symptoms that fall on a continuum from subthreshold to clinically significant, and a minimum age criterion in the range 55–65 years (Rodda et al., 2011). MDD is the most common psychiatric disorder in elderly people, showing a point prevalence of 4.6–9.3% (Meeks et al., 2011). In addition, subclinical symptoms such as minor depression and dysthymia are more common in old age, with a point prevalence of 10% (Pinquart et al., 2006). All of these forms of depression have been found to have a negative influence on the quality of life (Nelson et al., 2013). Late-life depressive disorders also increase disability (Nelson et al., 2013), are associated with poorer outcomes in clinically significant illnesses (Jiang et al., 2001), and a higher suicide rate (Conwell et al., 2002).

With regard to effective treatment of depression in elderly patients, practice guidelines identifies both antidepressants and psychotherapeutic interventions as a first line treatment for MDD, especially for mild to moderate depression, and a combination thereof or antidepressants alone for severe depression (American Psychiatric Association, 2010). Given that psychotherapy and pharmacotherapy did not show strong differences in effect sizes in elderly patients in a direct comparison (Pinquart et al., 2006), the authors recommend that treatment choice should be based on other criteria, such as contraindications, treatment access, or

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patient preferences. For neuropharmacological practice, selective serotonin reuptake inhibitors (SSRIs) and other second-generation antidepressants medications should be considered over monoamine oxidase inhibitors or tricyclic antidepressants (American Psychiatric Association, 2010; Rodda et al., 2011). Moreover, antidepressant use in elderly people with depression increased over the last years, mainly due to a growing SSRI-use (Sonnenberg et al., 2008). SSRIs have been shown to be superior to a placebo pill in controlled clinical trials and meta-analyses investigating late-life depression (Kok et al., 2012; Mittmann et al., 1997; Nelson et al., 2008). However, overall drug effects in elderly patients with symptoms of depression are only modest, with an odds ratio (OR)=1.40 (95% CI: 1.24–1.57) for response (i.e., ≥50% improvement from baseline on mood scales), and OR=1.27 (95% CI: 1.12–1.44) for remission (i.e., no longer meeting diagnostic criteria) versus placebo in a meta-analysis of 10 trials (Nelson et al., 2008).

With regard to possible moderators of pharmacological and placebo outcomes in depression, mixed-age studies have repeatedly shown that the mean differences between groups treated with antidepressant medication and placebo become larger as baseline severity increases (Fournier et al., 2010; Khan et al., 2002; Kirsch et al., 2008). It is unclear whether the increasing benefits, as severity increases, of drug treatment over placebo treatment are due to a decrease in the response to placebo treatment or an increase in the response to pharmacological intervention. The data reported by Kirsch et al. (2008) indicated that the increased benefit of drug treatment for severely depressed patients is related to a decrease in responsiveness to placebos, with no change in responsiveness to the drug. However, two meta-analyses have shown that initial severity predicted symptom improvement in adult patients who took antidepressant medication (Fournier et al., 2010; Khan et al., 2002). In the Khan et al. (2002) analysis, improvement as a function of baseline severity increased in drug groups but decreased in placebo groups. In Fournier et al. (2010), improvement as a function of severity increased significantly in both drug and placebo groups (as would be predicted by regression toward the mean), but the increase was significantly larger in the drug group. It should be noted that a re-analysis of the Kirsch et al. (2008) data set, which controlled for the effect of structural coupling (this occurs when baseline values and change score are coupled algebraically, thus possibly leading to an inflated association between the variables; Tu et al., 2004) concluded that baseline severity did not influence treatment outcome (Fountoulakis et al., 2013).

Studies looking at predictors of treatment outcome in elderly patients with depression are limited and most studies in this field do not focus on baseline depression severity. To date, symptom severity at baseline has not been shown to be a moderator of outcome in depressed elderly people. A meta-analysis by Gibbons et al. (2012) found that in a geriatric subgroup, baseline severity was not related to a positive treatment outcome for fluoxetine compared with placebo. Another meta-analysis found an association between initial severity and drug over placebo efficacy in elderly patients who had suffered from depression for at least 10 years, but not in the majority of patients, who had a shorter disease history (Nelson et al., 2013). However, there are several limitations to the reported meta-analyses. First, they rely on a limited number of studies, thus Gibbons et al. (2012) included 4 geriatric studies, whereas Nelson et al. (2013) included 10 trials of second-generation antidepressants in patients with late-life depression. Second, the authors included only a restricted range of baseline severity scores as they focused on MDD. However, only a minority of significantly depressed elderly patients fulfill the diagnostic criteria for depression, yet the rate of sub-threshold late-life depression rises with age and is responsible for comparable disability and distress (Pinquart et al., 2006).

Consequently, to assess treatment effects in late-life depression, a meta-analysis including a broader range of studies and taking minor depression and dysthymia into account is of a high relevance. With this background, we undertook a systematic review and meta-analysis to test the assumption that mean differences between antidepressant and placebo interventions become larger as baseline severity increases in a geriatric population.

2. Method

2.1. Search strategy and eligibility criteria

We performed searches in Cochrane, Embase, PsycINFO, PubMed, and Web of Science on studies published through September 30, 2014. Search terms were adapted to the electronic bibliographic databases and consisted of keyword combinations based on the inclusion criteria (for details see Appendix). In addition to the systematic search, the references of all included articles were reviewed.

We included peer-reviewed randomized, double-blind, placebo-controlled clinical trials reported in English or German comparing depressed elderly individuals in a placebo group with depressed elderly individuals in an intervention group receiving second-generation antidepressants (i.e., SSRI's and other novel atypical antidepressants). We classified antidepressants according to the Anatomical Therapeutic Chemical (ATC)[2] classification system of the World Health Organization as an internationally accepted standard of defining whether a drug counts as an antidepressant or not. Moreover, we grouped antidepressants as SSRI's or other novel atypical antidepressants in accordance with other meta-analyses (Anderson, 2000; Kok et al., 2012). The minimum age criterion was set at a mean or median age of 55 years, or described as elderly, geriatric or older adults.

Outcomes had to be reported as mean change in depressive symptoms on a continuous mood scale, such as the Hamilton Depression Rating Scale (HDRS; Hamilton, 1967) or Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979). We included only continuous outcome data, since dichotomizing continuous scores into categorical outcome data leads to a loss of information, reduces power and creates an artificial boundary (Altman and Royston, 2006; Moncrieff and Kirsch, 2005). Pre- and post-intervention data had to be available. We included studies investigating patients with MDD or subclinical depressive symptoms (i.e., minor depressive disorder or dysthymia) according to explicit, reliable, and reproducible diagnostic criteria, which were based on DSM-III, DSM-III-R, DSM-IV or DSM-IV-TR. However, we included one study where diagnostic criteria were not explicitly stated (Gerner et al., 1980). Medical comorbidities such as diabetes (Paile-Hyvärinen, Wahlbeck, & Eriksson, 2007), diagnosis of heart failure (Fraguas et al., 2010), or age-related macular degeneration (Brody et al., 2011) were not grounds for exclusion, as they are not neurological disorders.

Studies in which patients had depression following cerebrovascular disease (i.e., vascular depression and post-stroke depression), a cognitive impairment (i.e., moderate to severe dementia), or Parkinson's disease were excluded. We excluded studies investigating these neurological disorders because executive dysfunction and associated learning impairments in older patients with depression have been associated with a lower probability of antidepressant and placebo response (Alexopoulos et al., 2005; Benedetti et al., 2006a, 2006b). However, we included patients with mild cognitive impairment according to the Mini Mental-State Examination (MMSE > 19; Folstein et al., 1975) and two papers, which had not explicitly

[2] Available at: www.whocc.no. Accessed January 27, 2015.