

A Systematic Review and Meta-regression Analysis of Study Design Variables associated with Attrition in Randomised Controlled Trials of Antidepressants used in the Treatment of Major Depressive Disorder

Introduction

Major Depressive Disorder (MDD) is the number one psychological disorder in the western world. By 2020 it is predicted MDD will be the second most disabling condition worldwide behind heart disease. It is estimated that 1 in 5 adults in the United Kingdom (UK) show symptoms of depression. Antidepressants are currently the mainstay treatment for (MDD). In 2015, 61.0 million antidepressant items were prescribed in the U.K, which is 31.6 million (107.6%) more than in 2005.

Within the UK, over two dozen different antidepressants have been approved as safe and effective treatments for MDD. The National Institute for Health and Care Excellence (NICE) clinical guidance on depression in adults; concludes that antidepressants have largely equal efficacy and the choice should depend on the side-effect profile, previous experience of treatments, tendency to cause discontinuation symptoms, interactions and cost. Despite the availability of a multitude of different antidepressants, in practice more than 40% of patients on antidepressants prematurely stop treatment within three months. There is still a need for new novel antidepressants, with better efficacy, quicker onset of action and higher rates of remission and response in patients with MDD.

The need for new antidepressants is compounded during development, as up to 36% of participants within randomised controlled trials (RCTs) dropout of the trial. Attrition (dropout, withdrawal, loss to follow up, premature discontinuation) of 20% or greater raises concerns about the possibility of attrition bias and serious threats to validity. Whilst RCTs are mandatory to meet regulatory requirements for the approval of new antidepressants, there are no recommendations in the design of trials to reduce attrition. In particular, limited research exists investigating the association of study design variables (such as number of treatment arms, number of treatment assessments, fixed or flexible treatment schedule, control type, ratio of treatment allocation, number of study sites, trial duration, baseline depression severity, clinical setting, country of study location and sponsor type) with attrition. No studies have been undertaken examining study design variables relating to attrition of MHRA (UK) approved antidepressants. This review will aid researchers and clinical trial decision

makers, to predict attrition and subsequently make adjustments to the study design to minimise attrition and related threat to trial validity.

Aims

- To investigate study design variables associated with attrition in parallel double-blind, placebo and / or active comparator controlled RCTs of MHRA (UK) approved antidepressants used to treat Major Depressive Disorder.
- To generate a model to predict attrition in parallel double-blind, placebo and / or active comparator controlled RCTs of antidepressants used to treat Major Depressive Disorder.

Search Methods

Systematic reviews help to establish whether clinical findings are consistent and can be generalised across populations and settings. Data was gathered from a number of sources: electronic searches (Medline, Embase, Psychinfo, Cochrane and Google Scholar, COPAC); trial registries (including clinicaltrials.gov, EU Clinical Trials Register and WHO International Clinical Trials Registry); lastly pharmaceutical companies and the UK regulatory medication authority MHRA.

Selection Criteria

Study criteria included published and non-published parallel double-blind, placebo-controlled and / or active comparator(s) controlled randomised controlled trials of MHRA (UK) approved antidepressants used to treat Major Depressive Disorder. Adults aged over 18 years of age suffering from moderate or severe Major Depressive disorder were included.

Data Collection

The review author screened articles for inclusion, extracted data and analysed the results. Data extraction was completed using a modified data extraction form based on Cochrane Collaboration recommendations.

Main Results

The included trials had an overall mean attrition of 19.80%. Two predictive regression models were found to be significant. The first included two treatment arms ($p = 0.03$) and pharmaceutically sponsored studies ($p = 0.023$) significantly increased attrition, by 5.95% and 8.0% respectively. The second model from a sensitivity analysis found multi-site ($p < 0.001$), studies conducted in the USA ($p = 0.006$) and three or more treatment arms ($p = 0.045$) significantly reduced attrition by 24.36%, 6.66% and 4.5% respectively. Whereas large sample sizes increased attrition by 0.018% per added participant ($p = 0.047$).

Conclusion

The results of this review found the predictive model: multi-site, studies conducted in the USA, three or more treatment arms and large sample sizes as the more accurate predictive model out of the two. Although not tested as a possible predictor, placebo-controlled arms were significantly associated with decreased attrition. Importantly the nature of this review is a relevant topic and has helped to quantify the predicted attrition for studies either at the funding stage, design stage or for studies underway.

Despite the significance of this model it may not be feasible in practice to encompass all variables in the study design to reduce attrition. In particular conducting research in the USA alone or using smaller sample sizes would not be suitable or practical for licensing of new antidepressants. In parallel the research is restricted to defined population, drug and RCT design.

Prior to the bursary and completion of my Masters in Public Health (Health Service Research), I was unable to construct an effective research question, let alone a research proposal. I now have a fundamental understanding of research principals both quantitative and qualitative. A personal desire of mine prior to the course, was to gain the ability to conduct a systematic review. I have successfully completed two and feel confident going forward to not only use this research method but to critically appraise systematic reviews too. I am able to critique statistical evidence proposed by clinicians, whom challenge my ideas for Medicines Optimisation projects. I have broadened my network of professional contacts beyond the scope of pharmacy. I believe it is important to engage widely, in order to embrace future research opportunities. Whilst I was completing my dissertation, I have made effort to bridge links with our local universities. As a result I have been invited to join the Medicines Optimisation Research Group at Aston University. My ambitions are to combine my practicing role as a Clinical Commissioning Group pharmacist, with academia collaborative research to meet the needs of our local population. Whilst the degree has equipped me with research skills, in parallel I have gained Public Health expertise too, with the two areas working synergistically. To endorse my Public Health skills I have networked with our Local Authority to scope possible areas of future research interest in collaboration with academia. Moreover, I believe the bursary and qualification has opened doors to a chapter in my life, which will develop my current role as a pharmacist, into a role with more fulfilling and opportunistic outcomes.