European Psychiatry 53 (2018) 66–73

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Original article

Effectiveness of watchful waiting versus antidepressants for patients diagnosed of mild to moderate depression in primary care: A 12-month pragmatic clinical trial (INFAP study)

M. Iglesias-González[a,b,d], I. Aznar-Lou[c,d], M.T. Peñarrubia-María[d,e,f], M. Gil-Girbau[c,f,i], R. Fernández-Vergel[e,f], J. Alonso[d,g,h], A. Serrano-Blanco[a,c,d,*], M. Rubio-Valera[c,d,i]

[a] Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat, Spain
[b] School of Medicine, University of Barcelona, Barcelona, Spain
[c] Teaching, Research & Innovation Unit, Institut de Recerca Sant Joan de Déu, Esplugues de Llobregat, Spain
[d] Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública, CIBERESP, Madrid, Spain
[e] SAP Delta Llobregat, DAP Costa Ponent, Institut Català de la Salut (ICS), Catalonia, Spain
[f] Fundació Idiap Jordi Gol i Gurina, Barcelona, Spain
[g] Health Services Research Unit, IMIM-Hospital del Mar Medical Research Institute, Barcelona, Spain
[h] Pompeu Fabra University (UPF), Barcelona, Spain
[i] School of Pharmacy and Food Sciences, Universitat de Barcelona, Barcelona, Spain

ARTICLE INFO

Article history:
Received 28 March 2018
Received in revised form 19 June 2018
Accepted 19 June 2018
Available online xxx

Keywords:
Depression
Watchful waiting
Active monitoring
Primary care
Antidepressants

ABSTRACT

Background: Although mild to moderate major depressive disorder (MDD) is one of the main reasons for consulting a general practitioner (GP), there is still no international consensus on the most appropriate therapeutic approach.
Methods: The aim of this study is to evaluate the clinical effectiveness of watchful waiting (WW) compared with the use of antidepressants (ADs) for the treatment of mild to moderate depressive symptoms in 263 primary care (PC) usual-practice patients in a 12-month pragmatic non-randomised controlled trial. Both longitudinal and per-protocol analyses were performed, through a multilevel longitudinal analysis and a sensitivity analysis.
Results: We observed a statistically significant time x treatment interaction in the severity of depression (Patient Health Questionnaire, PHQ-9) and disability (World Health Organization Disability Assessment Schedule, WHODAS) in favour of the AD group at 6 months but not at 12 months. The effect size of this difference was small. No statistically significant differences were observed between groups in severity of anxiety (Beck Anxiety Inventory, BAI) or health-related quality-of-life (EuroQol-5D, EQ-5D). Sensitivity analysis and per-protocol analysis showed no differences between the two groups in any of the evaluated scales.
Conclusions: Superiority of either treatment (WW and AD) was not demonstrated in patients treated for depression in PC after one year of follow-up.

1. Introduction

Mild and mild-moderate major depressive disorder (MDD) is one of the most important reasons for consulting a general practitioner (GP) and it will be among the three leading causes of disease burden by the year 2030 [1]. There is a lack of international consensus on the most appropriate therapeutic approach and the best strategy for implementation in Primary Care (PC). While, in some countries, pharmacological treatment with antidepressants (ADs) is recommended as an acute-phase treatment for patients with mild to moderate symptoms [2]; in most European countries a watchful waiting (WW) approach seems to be the first treatment step [3–5].

WW, also known as active monitoring or supportive care, has been described as an agreement between the clinician and the patient not to immediately treat the condition with ADs but to intermittently reassess its status during a specific follow-up period [6]. In common with most European guidelines for the treatment of depression, the Catalan Clinical Guideline [4] recommends that

* Corresponding author at: C/ Doctor Antoni Pujadas, 42, 08830, Sant Boi de Llobregat, Barcelona, Spain.
E-mail address: aserrano@pssjd.org (A. Serrano-Blanco).

http://dx.doi.org/10.1016/j.eurpsy.2018.06.005
0924-9338/

patients treated in PC should be regularly visited by GPs and offered a variety of non-pharmacological interventions (low-intensity psychosocial and psychological interventions such as problem-solving techniques, active listening, counselling, brief or computerised cognitive behavioural therapy, or medical education) while closely monitoring clinical progress. Studies show that this treatment approach is limited due to barriers including the clinician's high care burden and lack of time, knowledge of psychotherapy and availability of mental health professionals for referral [7].

Our recent systematic review found only three studies properly assessing the clinical effectiveness of WW compared with ADs when mild and mild-moderate MDD was treated in PC. No statistically significant differences in effectiveness between the two treatment arms were found in any of the articles when the main analysis was conducted (longitudinal analysis) [8]. The small sample sizes may have limited the capacity of these studies to detect statistically significant differences between groups.

The aim of this study is to evaluate the clinical effectiveness of WW compared with the use of ADs for the treatment of mild-moderate depressive symptoms in real PC practice.

2. Methods

2.1. Study design

This was a 12-month follow-up naturalistic prospective controlled trial comparing patients that received AD drugs with those who received WW. The study was approved by our institution (PSSJD: EPA-24-12; IDIAP: 5013-002). The detailed study protocol has been published elsewhere [9].

2.2. Setting and participants

The study was conducted in 12 PC centres in the province of Barcelona (Catalonia, Spain) and 68 GPs participated in the recruitment of patients.

Prior to the study, GPs received a three hour-training session on the study protocol, diagnostic criteria for depression, and national guidelines for the treatment of MDD in PC.

GPs recruited patients for the study from their daily list of patients attending the practice. Eligible patients were adults ($\geq$18 years-old) diagnosed with a first or recurrent new episode (new diagnosis or relapse) of mild to moderate MDD according to the GP's clinical judgement (due to the study design, there was no need for structured clinical diagnosis through standardised assessment scales). Patients were excluded if they had taken AD medication in the previous 60 days, had taken antipsychotics, lithium or antiepileptics in the previous six months, presented psychotic or bipolar disorder, had a history of drug abuse or dependency, had cognitive impairment that prevented an assessment interview, or refused to provide signed informed consent.

2.3. Interventions

In accordance with the study's naturalistic design, GPs used their professional clinical judgment to recommend a treatment option to the patient. Patients were recommended a WW approach or pharmacological treatment with ADs.

Patients in the WW group agreed with the GP not to immediately treat the condition with ADs but to closely monitor the symptoms through a series of follow-up visits. In line with the Catalan Guideline [4], a first follow-up visit was scheduled to take place within the following 2 weeks. The guideline recommends from six to eight follow-up visits over 10–12 weeks, where GPs can consider non-pharmacological interventions. It also recommends structured, supervised exercise programmes of moderate intensity. As part of the stepped care model, in the case that the patient's condition does not improve, the GP can intensify the treatment and initiate ADs. The number of visits following recruitment by the GP was used to monitor adherence to WW.

Patients in the AD group received pharmacological treatment with SSRIs (selective serotonin reuptake inhibitors), particularly with citalopram, sertraline, paroxetine or fluoxetine. Adherence to ADs was monitored through pharmacy records and patients' self-reported adherence (using the 4-item scale developed by Morisky et al. [10].

2.4. Outcomes

Sociodemographic data were collected on study commencement: age, gender, marital status, education and employment status.

The following outcomes were assessed at baseline, six and twelve months by an external researcher. The primary study outcome was the effectiveness of each treatment, WW or ADs, measured in terms of depression severity. This was assessed using the Patient Health Questionnaire 9-item depression module (PHQ-9) [11,12]. The scale consists of nine items scored from 0 to 3, with a summed score that ranges between 0 (no symptoms of depression) and 27 (all symptoms of depression every day): 0–4 indicates minimal symptoms; 5–9 mild depression symptoms; 10–14 moderate symptoms; 15–19 moderate-severe symptoms; and 20–24 severe symptoms.

Diagnosis according to DSM-IV criteria was not used as an inclusion criterion. However, clinical diagnosis according to DSM-IV criteria was assessed using the research version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [13]. The mood and anxiety disorder modules were used.

Severity of anxiety was evaluated through the Beck Anxiety Inventory (BAI), which is a twenty-one item self-report inventory ranging from 0 (minimal level of anxiety) to 63 (severe anxiety) [14,15].

The Spanish version of the EuroQol-5D-3 L (EQ-5D) was used to measure health-related quality of life [16,17]. The EQ-5D generates a health tariff that is anchored in 1.000 (best health state) and 0.000 (being dead).

The 12-item interviewer-administered version of the World Health Organization Disability Assessment Schedule (12-item WHO-DAS 2.0) was used to assess disability [18]. Total scores range between 0 and 100, with higher scores indicating a greater degree of disability.

Cognitive representation of medication was assessed using the Beliefs about Medicine Questionnaire (BMQ) [19,20]. Total scores range between 8 and 40. Higher scores represent more negative beliefs about medicines.

Chronic physical conditions were assessed using a "yes" or "no" check-list.

See study protocol for more detailed information on the administered scales [9].

2.5. Analysis design/strategy

Both intention to treat (ITT) analysis (all patients were included in the analysis in the group to which they were allocated independently of the treatment they finally received) and per-protocol (PP) analysis (including only those patients who adhered to the treatment originally allocated) were performed. Adherence in the WW group was defined as receiving at least 3 follow-up visits and at least one of the recommended interventions (psychoeducation, problem-solving therapy and/or physical exercise). Adherence in the ADs group was defined as having a mean