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Research report

Are multiple physical symptoms a poor prognostic factor or just a marker of depression severity? Secondary analysis of the GenPod trial

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ABSTRACT

Background: Using data from the GenPod trial this study investigates: (i) if depressed individuals with multiple physical symptoms have a poorer response to antidepressants before and after adjustment for baseline Beck Depression Inventory II (BDI-II); and (ii) if reboxetine is more effective than citalopram in depression with multiple physical symptoms.
Methods: Linear regression models were used to estimate differences in mean BDI-II score at 6 and 12 weeks.
Results: Before adjusting for baseline BDI-II, the difference in mean BDI-II score between no and multiple physical symptoms was 4.5 (95% CI 1.87, 7.14) at 6 weeks, 4.51 (95% CI 1.60, 7.42) at 12 weeks. After adjustment for baseline BDI-II, there was no evidence of a difference in outcome according to physical symptoms with a difference in mean BDI-II of 2.17 (95% CI −0.39, 4.73) at 6 weeks and 2.43 (95% CI −0.46, 5.32) at 12 weeks. There was no evidence that reboxetine was more effective than citalopram in those with multiple physical symptoms at 6 (P=0.18) or 12 weeks (P=0.24).
Limitations: Differential non-adherence between treatment arms has the potential to bias estimates of treatment efficacy.
Conclusion: Multiple physical symptoms predict response to antidepressants, but not after adjustment for baseline depression severity. Physical symptoms could be a marker of severe depression rather than an independent prognostic factor and depression should be considered in patients with multiple physical symptoms. Treatment with reboxetine conferred no advantage over citalopram in those with physical symptoms, and it is less well tolerated.

1. Introduction

Physical symptoms, which are distinct from those considered to be symptoms of depression (for example sleep and appetite disturbance) are common in depression (Haug et al., 2004; Bair et al., 2003). These types of symptoms (for example a change in bowel habit or pain) are often given as the presenting complaint as opposed to low mood (Bridges and Goldberg, 1985; Kirmayer et al., 1993; Keeley et al., 2004). Depressed patients are 3–7 times more likely to develop multiple physical symptoms than those who are not depressed (Hotopf et al., 1998). In many cases, no physical explanation for these symptoms is found and even when a disease state is present, the nature or degree of the symptoms may not correlate with the known pathology. A reduction in clinician's ability to detect depression has been shown with increasing levels of such physical symptoms (Bridges and Goldberg, 1985; Kirmayer et al., 1993; Bair et al., 2003). It has been estimated that 60% of previously undetected depression cases could have been identified if all primary care patients presenting with pain conditions were examined for possible depression (Katon, 1984). Patients in this group are therefore at risk of receiving an inaccurate diagnosis (Kirmayer et al., 1993; Bridges and Goldberg, 1985), are likely to use more healthcare resources (Bair, 2004; Fritzsche et al., 1999; Widmer and Cadoret, 1978) and are at risk of potential iatrogenic harm.

A 'somatic depression' has been proposed (Silverstein and Patel, 2011) that is more prevalent in women. The authors found

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that those who exhibited depression accompanied by multiple physical symptoms had a poorer response to antidepressants compared with the other depressed participants. Other studies have supported the theory that patients who have a depression with multiple physical symptoms have a poorer outcome in response to antidepressant treatment (Papakostas et al., 2003; Papakostas et al., 2008; Bair, 2004; Hoencamp et al., 1994) problem-solving therapy (Huijbregts et al., 2010) and collaborative care (Huijbregts et al., 2013). The Papakostas study of 2008 was a large ($n=570$), flexible dose, open-label trial of fluoxetine for major depressive disorder (MDD, as defined by DSM-IV). Using a self-report Symptom Questionnaire (Kellner, 1987) they found that the severity of somatic anxiety symptoms of MDD at baseline predicted a worse outcome with fluoxetine. The ARTIST study (Bair, 2004) also demonstrated that pain is a strong predictor of poor depression outcome.

The association between depression and pain becomes stronger as the severity of either condition increases (Bair et al., 2003). Therefore, an alternative theory is that patients with multiple physical symptoms have a more severe depression at baseline and therefore a poor prognosis. Denninger et al. (2006) reported that baseline somatic scores are related to baseline severity of depression. Severe depression at baseline predicts lower rates of remission with antidepressant treatment (Rush et al., 2008; Trivedi et al., 2006). This means that in order to understand the relationship between multiple physical symptoms in depression and prognosis with antidepressant treatment, the baseline severity of the depression must be taken in to account and adjusted for in the analysis. This has not been done in some of the studies that have predicted a poor outcome for depression with multiple physical symptoms (Silverstein and Patel, 2011; Papakostas et al., 2003).

Moderators are factors that predict differential treatment response. Identifying a moderator of antidepressant effect in patients with multiple physical symptoms has obvious clinical and economic value (Trusheim et al., 2007). Matching patients to treatments using particular patient characteristics (such as genetic polymorphisms or symptom profile) is called stratified or personalised medicine. Its benefits have been demonstrated with a number of anticancer medications (Trusheim et al., 2007). Psychiatrists commonly select antidepressants based on symptom profile (Zimmerman et al., 2004), but due to an absence of established clinical moderators (Simon and Perlis, 2010), there is limited evidence to inform this choice.

It is thought that brain mechanisms concerned with depression and pain both involve the monoamine projections from the midbrain (Bair et al., 2003). Noradrenaline is implicated in the aetiology of MDD and has been studied extensively (Ressler and Nemeroff, 1999). There is some evidence to suggest a relationship between noradrenaline and depression with physical symptoms (Fava, 2003). Dual acting agents (with an effect on serotonin and noradrenaline) have been reported as superior to selective serotonin re-uptake inhibitors (SSRIs) in treating the somatic symptoms associated with depression (Delgado, 2004; Fishbain, 2000). Kang et al. (2009) found that venlafaxine (a serotonin–noradrenaline re-uptake inhibitor) and mirtazipine (a noradrenergic and specific serotonergic receptor antagonist antidepressant) improved depressive symptoms in those with a diagnosis of MDD and somatic symptoms. Based on this evidence, the presence of physical symptoms could be a moderator of treatment in those with depression.

Stratified medicine aims to personalise treatment based on characteristics of an individual. One way of providing evidence to stratify antidepressant treatment is to compare two treatments in a group of patients and see if any particular characteristic moderates the relationship between treatment and outcome (18). The GenPoD trial looked at two potential moderators of response to antidepressants; (1) a polymorphism in the 5HTTLPR gene (the serotonin transporter gene) (Lewis et al., 2011) and (2) depression severity (Wiles et al., 2012). There was no evidence that either moderated treatment response. In this study, we used GenPod data to investigate the following hypotheses: (1) that those with multiple baseline physical symptoms do worse with antidepressant treatment at 6 and 12 weeks; and (2) that reboxetine is better than citalopram in treating patients with depression who have multiple baseline physical symptoms.

2. Methods

2.1. GenPoD trial

This is a secondary analysis of data from the GenPoD trial, whose trial protocol and main results are published elsewhere (Lewis et al., 2011; Thomas et al., 2008). In brief, GenPoD is a multi-centre Randomised Controlled Trial (RCT) conducted in Bristol, Birmingham and Newcastle, UK. Participants were patients aged 18–74 years referred to the trial by their General Practitioner (GP) following agreement to prescribe an antidepressant. Eligibility criteria included a diagnosis of ICD-10 depressive episode F32 from the Clinical Interview Schedule-Revised (CIS-R) (Lewis et al., 1992) and a Beck Depression Inventory II (BDI-II) (Beck At, 1961) score of ≥ 15. Exclusion criteria included having taken an antidepressant in the two weeks preceding baseline assessment and those who could not complete the self-administered scales. The GPs excluded those with medical contraindications to antidepressant treatment, those with psychosis, bipolar affective disorder or major substance or alcohol abuse. Chronic physical illness was not a contraindication to participation.

2.2. Randomisation

Participants were randomised to receive either reboxetine (4 mg twice daily) or citalopram (20 mg once daily) after giving informed consent. Randomisation was conducted using a computer-generated code, centrally administered and communicated by telephone. The randomisation was stratified by symptom severity (CIS-R <28 or ≥ 28) and centre using variable block sizes. Neither participants nor researchers were blinded to allocation. The researcher gave the medication to the participant. Initially, those prescribed reboxetine were given a dose of 2 mg twice daily, which was increased to 4 mg twice daily after four days. Participants were advised to contact their GP if they wished to increase their dose.

2.3. Depression measures

The CIS-R was completed at baseline. This is a fully structured interview measuring common psychological symptoms present in the week prior to interview. It encompasses 14 symptom groups with the aim of identifying and characterising the symptoms of anxiety and depression (Lewis et al., 1992). The BDI-II measures the severity of depression and was completed at baseline, 6 and 12 weeks.

2.4. Exposure measures

The exposure variable of interest in this study was the presence of physical symptoms at baseline. This was measured using a modified form of the Toronto Side Effects Scale (Vanderkooy et al., 2002). For this purpose, the scale was used to measure physical symptoms at baseline before the participants had started the study medication. The modified scale used is included in the supplementary material (Supplementary Fig. 1). Symptoms that