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REVIEW ARTICLE

Evidence for the treatment of moderate depression: a systematic review

D. Aherne, A. Fitzgerald, C. Aherne*, N. Fitzgerald, M. Slattery and N. Whelan

Counselling Department, University of Limerick, Limerick, Ireland

Objectives. This study aims to investigate existing evidence for the effectiveness of psychological treatments and/or antidepressant medication as a treatment for those diagnosed with moderate levels of depression.

Methods. A PRISMA systematic review of articles using electronic research databases (2000–2014) was conducted to identify studies investigating the effectiveness of psychotherapy and/or medication as a treatment for people with moderate levels of depression. Search terms included moderate depression, psychotherapy and/or medication, depressive disorders, antidepressants, psychotherapy, mental health services, and randomized-controlled trial (RCT). The included studies were then assessed, extracted, and synthesised.

Results. A total of 14 studies met the inclusion criteria (11 RCTs and three additional studies) for this review. The findings of the systematic review indicate that there is limited evidence available specific to the treatment of moderate depression and that this research seems to suggest that psychotherapy or combined treatment has a beneficial effect.

Conclusions. Given that depression is one of the biggest challenges the world faces at present, further research is required to examine the effectiveness of treatment for different levels of depression severity.

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Key words: Antidepressant medication, depression, psychological treatments, systematic review, treatment.

Introduction

Depression is one of the most prevalent and disabling of psychological problems related to diminished quality of life and role functioning, medical morbidity and mortality (Spijker *et al*. 2004; Üstün *et al*. 2004; Paykel *et al*. 2012). There are over 350 million people experiencing depression annually [World Health Organisation (WHO), 2012]. In addition, depression is a significant public health concern across all regions of the world (Bromet *et al*. 2011). Within an EU context, research carried out by Wittchen *et al*. (2011) reported that ~38% of the EU population (164.8 million people) struggle with mental health difficulties each year. Major depression affects 30 million people in the EU, becoming the most burdensome disorder of all diseases. The existing evidence for the effectiveness of psychological treatments and/or antidepressant medication treatments for those diagnosed with moderate levels of depression is ambiguous and a review of such evidence is, therefore, warranted.

Based on severity of symptoms, depression can be reported and experienced at different levels of severity. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) classifies major depressive disorder into three distinct levels, namely mild, moderate, or severe, based on the intensity of depressive symptoms, symptom count, and degree of functional impairment (American Psychiatric Association, 2013). Studies investigating depression in the general population have reported that the prevalence of Major Depressive Disorder (MDD) for 12 months as 6.6%, affecting between 13.1 and 14.2 million US adults. Kessler *et al*. (2003) has shown that, of those with MDD, 10.4% were reported as 'mild', 38.6% 'moderate', and 51% 'severe or very severe' depression. Another study by Kessler *et al.* (2005) reported that of 9282 respondents, 6.7% identified as depressed and within that group, 30.4% reported 'severe' depression, 50.1% 'moderate' depression, and 19.5% 'mild' depression. Epidemiological data depicting the severity of depression are largely restricted to populations from North America, and there is a need for data depicting the severity of depression from a representative European sample.

Many treatments have been recommended for depression including different medications, a range of psychological therapies, exercise regimes, and alternative remedies. One of the influencing factors in determining the efficacy of any or all of these treatments is the level of severity of the depressive symptoms [see National Institute of Care and Excellence (NICE), 2009].

* Address for correspondence: C. Aherne, Counselling Department, University of Limerick, Limerick, Ireland.
(Email: declan.aherne@ul.ie)

Severity of depression as a significant factor in treatment

The severity of depression is a significant factor in examining treatment effectiveness. The effectiveness of antidepressant medication and placebo was investigated by Fournier *et al*. (2010), which concluded that the benefits of antidepressant medication over placebo were only substantial for patients with severe depression. Similar studies by Khan *et al.* (2002) and Kirsch *et al*. (2008), identified that clinically meaningful improvements could only be achieved where initial Hamilton Depression Rating Scale (HDRS) scores exceeded 28 (where a score of 23 is indicative of very severe depression). Fournier *et al*. pointed out that there is a paucity of investigations of the true effects of antidepression medication as a treatment for patients with less than severe depression. Fournier *et al*. also commented that evidence concerning the effects of antidepressant medication in patients with mild and moderate MDD has been sparse. An important conclusion of these findings was that high levels of depression symptom severity was required for clinically meaningful drug/placebo differences to emerge. These findings are surprising, particularly, given the evidence that the majority of patients receiving antidepressant medication in clinical practice present with scores below this level of severity. Fournier *et al*. concluded that prescribers, policy makers, and consumers might not be aware that the efficacy of medications has been largely established on the basis of studies that have included only those individuals with more severe forms of depression.

Given that research suggests that a significant proportion of the population experiencing depression are identified as moderately depressed (e.g. Kessler *et al*. 2005), the present paper systematically reviews studies of treatment effectiveness for adults experiencing depression at this level of severity.

Current treatment guidelines for moderate depression

The NICE guidelines provide recommendations for professional standards of practice in relation to a range of psychological difficulties in the United Kingdom, and are based on the DSM-V [American Psychiatric Association (APA), 2013]. NICE (2009) guidelines state, 'if you have moderate or severe depression, you should be offered both an antidepressant and a psychological treatment'. The present paper examines the evidence supporting this recommendation by carrying out a systematic review of all studies on the treatment of moderate depression over a 16-year period. To date, there is no evidence to indicate that treatment intervention for moderate depression is the same as that for either mild or severe depression, it is important, therefore, that evidence for the treatment efficacy of this specific level of depression severity is examined.

Levels of severity of depression in research designs

Studies of depression tend to examine an amalgamation of severity levels within their samples, such as 'mild to moderate', and 'moderate to severe' (e.g. van der Lem *et al.* 2012). The criteria used do not identify moderate depression as a specific severity level to be examined. For example, the specific severity band of depression was not a consideration in Cuijpers *et al.* (2009) meta-analysis on treatment effectiveness for chronic depression. Similarly, Cuijpers *et al.* (2010*a*) looked at the effects of psychotherapy for depression and used bands of 'moderate to severe', 'severe', and 'mild to moderate depression'. No conclusions were made in relation to moderate depression. In another meta-analysis of 16 randomised-controlled trials (RCTs) examining the effects of psychotherapy on chronic depression, Cuijpers *et al*. (2010*b*) included studies where participants met diagnostic criteria for 'a depressive disorder' but likewise no reference was made to a specific categorisation to be examined. More recently, Cuijpers *et al*. (2014) reported that combined treatments were found to be more effective than either psychotherapy or medication alone and the criteria for inclusion used was 'depressive disorder'. In this meta-analysis, the effect size was reported to be influenced by the severity of depression. Individual depression scores, however, were not considered, but rather an average score was taken for the sample as a whole. Meta-analytic studies have been carried out to establish guidelines on the treatment for different levels of depression. For example, Fournier *et al*. (2010) conducted a meta-analysis of RCTs of antidepressants in the treatment of the different severity levels of depression conducted between 1980 and 2009. In this study, the sample chosen was grouped into 'mild to moderate', 'severe', and 'very severe' based on the HDRS scores offered by the APA. Notably, there were no known studies on 'moderate' depression reported.

Numerous systematic reviews have also been carried out in order to assist with clarifying treatment effectiveness for depression. Conclusions, however, refer to MDD rather than the different severity levels of depression (e.g. Khan *et al*. 2001; Zhou *et al*. 2014; Linde *et al*. 2015). To date, however, there are no known systematic reviews carried out on treatment effectiveness solely for moderate depression.

In summary, the different bands of depression have been predominantly amalgamated so that moderate depression has been either considered in combination with mild depression or with severe depression, but not as a stand-alone band of depression. Past research has

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predominantly focussed on the efficacy of pharmacotherapy and psychotherapy treatments for depression across a wide range of symptom severity in individuals diagnosed with depression, without paying particular attention to the three main categories of depression severity stated in DSM-V. The present paper, therefore, addresses a gap in the literature by systematically reviewing the efficacy of treatments for those diagnosed with moderate levels of depression.

Method

Inclusion criteria: data sources and search strategy

The present review examines studies of the treatment effectiveness for moderate depression alone. The systematic review was written up according to the PRISMA standard (a protocol used to evaluate systematic reviews; Moher *et al*. 2015). In order to identify studies which included antidepressant pharmacotherapy and psychotherapy (psychological treatment), a search of EBSCO and SCOPUS was carried out that included the following databases: Medline, Cumulative Index to Nursing and Allied Health Literature, Psych Articles, Psych Info, Omnifile, Amed, Academic search complete, Social Sciences, UK and Ireland reference centre. The final database to be used was the Cochrane Database of Systematic Reviews. All searches were restricted to the period from January 2000 to January 2014 and included all keywords ordered as the following; 'Moderate Depression' and/or 'Psychotherapy', and/or 'Medication'. Subject headings included were as follows: depression, depressive disorders, antidepressants, psychotherapy, mental health services, and RCTs. Search terms for moderate depression, treatment, psychotherapy, medication (antidepressants), and combination treatments were explored.

Primary studies, including RCTs and systematic reviews that investigated pharmacotherapy, psychotherapy alone, and pharmacotherapy and psychotherapy combined, with moderate depression alone, were retained. Studies where moderate depression was investigated in combination with mild and/or severe depression or other types of depression were therefore excluded from this review. In order to classify the definition of psychological treatment, our review followed the system of Rush & Thase (1999) who regard interpersonal, cognitive, behavioural, and psychodynamic therapies as psychological treatment. Although each of these therapeutic interventions hold very different conceptual backgrounds, the rationale for including them all is that each treatment is focussed on the reduction in symptoms of depression and the prevention of reoccurrence and relapse (Pampallona *et al.* 2004).

Study selection

Published and unpublished studies were eligible. Studies that included the treatment of moderate depression solely were selected. All the abstracts of the papers for inclusion in the review were screened and the full paper was obtained where there was insufficient information in the abstract.

Data extraction and quality assessment

The quality of the studies were assessed in terms of methodological strength and limitations, that is recruitment procedure, sample size, and sufficient reporting of primary outcomes. Specific to RCTs, random allocation sequences, concealment of allocation sequences, blinding, and reporting of proportions of patients lost to follow-up were also assessed. An ad hoc form was designed for data extraction including information such as setting, number of participants, diagnosis, sex, mean age, type of intervention, measures used, and antidepressant drug administered. A data extraction table was developed detailing each of the variables of interest for the present review. Using the extraction table as a template, two reviewers extracted relevant data from all of the articles. After completion of the initial data extraction, a second independent reviewer checked the accuracy of the extracted data. In the case of disagreements between two reviewers, a third reviewer examined the full article to make a determination about whether to include or exclude the article. Review authors carefully considered the potential limitations of the included studies. Methodological appraisal of each study was conducted according to PRISMA standard.

To assess study quality, six quality rating criteria were selected in order to inform whether or not each study should be rated as high, medium, or low quality. These criteria were selected based on the researchers reading of what elements should be required to ensure high research quality (mainly based on a RCT design). The six criteria were as follows: (1) the study addressed an appropriate and clearly focussed question, (2) random assignment allocation, (3) participants and investigators were 'blind' about treatment allocation, (4) treatment and control groups were equivalent at baseline, (5) the only difference between groups was the treatment under investigation, and (6) all relevant outcomes were measured in a standard, valid and reliable way. A quality checklist table was developed based on these criteria. Two reviewers independently assigned a quality rating ('yes', 'no', 'can't say') to each study; results were compared and differences discussed until agreement was obtained. The decision for low, medium, and high-quality ratings were as follows: (a) low: two criteria were present and four were not/can't say, (b) medium: four criteria were present and

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two were not/can't say, and (c) high: all six criteria were met.

Results

Data extraction

From the initial searches on depression, over 78 800 articles were identified investigating depression. Based on broad inclusion criteria, that is studies of the treatment effectiveness solely for moderate depression between January 2000 and January 2014, 278 were relevant for further screening. The identified abstracts lead to the exclusion of 264 papers due to the inclusion of mild and severe severity depression levels, and the inability to reach the set inclusion criteria, namely primary studies including RCTs and systematic reviews that investigated pharmacotherapy, psychotherapy, and combination treatments with moderate depression. For each of the 14 remaining studies meeting our inclusion criteria, available information regarding the sample (i.e. sample size, basic demographics, and recruitment setting), study design, intervention type, and any descriptive findings related to behavioural and mental health outcome variables (see Table 1) were extracted.

A total of 14 studies with a total of 1743 participants met the inclusion criteria. Five of the studies used the Hamilton Depression Scale (HAMD-17) to measure the levels of moderate depression in the sample. The Beck Depression Inventory (BDI) was also used as a measure in five of the studies reviewed, with the remaining studies using measures such as The Center for Epidemiologic Studies Depression Scale (CES-D) and the ICD-10 Guide for Depression Diagnosis. Six of the studies examined medical treatments (including herbal), four studies examined psychological treatments, and a further four studies examined combined treatments of both medical and psychological interventions.

Study quality

With regard to study quality, the methodological quality of the 14 studies included in this review was standard. Of the 14 studies, eight studies were rated as high quality, while six studies were rated as medium. For those studies rated as medium, all met at least four of the six quality criteria; three did not blind the investigators and participants to treatment allocation, while two studies did not contain sufficient information to permit assessment. Two of the studies rated as medium did not randomly assign participants to treatment conditions. A bias check was also carried out on all studies with no reference to bias mentioned in any study, with the exception of Bastos *et al*. (2013) who employed bias-adjusted κ statistic.

Medical interventions

Of the six studies which investigated the effectiveness of medical interventions to treat moderate depression, four investigated the effectiveness of herbal remedies including Hypericum extract (St. Johns Wort) and Jieyu Pill (Chinese medicine) compared to traditional antidepressants (Uebelhack *et al.* 2004; Gastpar *et al.* 2005, 2006; Yeung *et al*. 2014). Each of these studies found that the herbal remedy was as effective as antidepressants when treating moderate depression. One study examined the effectiveness of pharmacotherapy in treating moderate depression when compared with the combination of pharmacotherapy and an aerobic training programme (Cerda *et al.* 2011) and found a decrease of depression symptoms only when the aerobic training programme was included. One study solely investigated the effectiveness of antidepressants in the treatment of moderate depression when compared with a placebo (Klein *et al*. 2014). The results indicated no significant difference between treatment and placebo groups in cases of moderate depression.

Psychological interventions

Four studies focused on psychological interventions such as cognitive behavioural therapy (CBT). Results showed CBT to be effective in reducing moderate depressive systems when used as an individual treatment, compared with usual care and a control condition (Antoni *et al*. 2001; Le *et al.* 2011; Carter *et al.* 2013). Results also indicated that CBT was effective in treating moderate depression when integrated with other forms of psychotherapy (Hamamci, 2006).

Combined interventions

Of the 14 studies that were included in this review, two studies investigated antidepressants and psychological interventions combined as an effective treatment. Stötter *et al*. (2013) investigated the effectiveness of an 8-week mindfulness intervention with antidepressants compared to antidepressants treatment only. Results showed that the use of mindfulness therapy demonstrated significant additional benefits in the treatment of moderate depression when combined with the use of antidepressants. Bastos *et al.* (2013) investigated the use of long-term psychodynamic therapy (LTPP) alone, pharmacotherapy alone and both combined. Results indicated that LTPP and pharmacotherapy combined were more effective in modifying specific areas of cognition than antidepressants alone or LTPP alone, in patients with moderate depression. Results of this systematic review also indicated that the use of self-help and biblio-therapy were effective in reducing the symptoms of moderate depression. Songprakun &

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Table 1. *Studies in the review that matched inclusion criteria*

Study[a]	Intervention	Design	Sample (Male:female) Mean age	Assessment tools	Primary outcome
Medical					
Cerda *et al.* (2011) Spain	Control group; pharmacotherapy (Fluoxetine 20 mg) *v.* study group; pharmacotherapy + aerobic training for 8 weeks, 3 days/week	Pre and post RCT	n = 82 (0:100) 32.4 years	BDI & ICD-10 Guide	An aerobic training programme as a complementary therapy diminishes depressive symptoms
Gastpar *et al.* (2006) Germany	6-week treatment with either 900 mg Hypericum extract, 20 mg Citalopram or placebo once/day	RCT	n = 388	HAMD-17	Hypericum extract STW3-VI is a good alternative to antidepressants in the treatment of outpatients with moderate depression
Gastpar *et al.* (2005) Germany	12 weeks with 612 mg Hypericum extract *v.* 50 mg Sertraline once/day. A total of 161 patients were treated after week 12 for additional 12 weeks.	RCT	n = 200	HAMD-17	Hypericum extract STW3 is therapeutically non-inferior to Sertraline after the first 12 weeks of interventions
Klein *et al.* (2014) Canada	Citalopram or placebo administered to HIV–HCV coinfected patients	RCT	n = 76 (66:10) 46.4 years	BDI-II	Incidence of moderate depression did not differ significantly by group
Tao (2006) China	Jieyu Pill treatment group 4 g ×3 times/for 6 weeks *v.* Venlafaxine extended release (ER) treatment group 75 mg once/day for 6 weeks.	RCT	n = 86	HAMD-17	The curative effect of Jieyu Pill in the treatment of moderate depression is the same as venlafaxine ER
Uebelhack *et al.* (2004) Germany	Hypericum extract STW 3-VI 900 mg once/day *v.* placebo	RCT	n = 140 (46:94) 45 years	HAMD-17	Hypericum extract STW 3-VI in a once-daily dosing regimen is an effective option for patients with moderate depressive disorder
Psychological					
Antoni *et al.* (2001) United States	Study group; 10-week group cognitive behavioural stress management	Single study	n = 100 (0:100) 50.2 years	CES-D scale	Intervention reduced prevalence of moderate depression
Carter *et al.* (2013) United States	CBT-I in chronically bereaved hospice nurses	Single study	n = 9 (1:8) 54 years	CES-D scale	The CBT-I had a positive effect on sleep onset latency, total sleep time, and sleep efficiency scores at 3 weeks post-intervention
Hamamci (2006) Turkey	Study group; attended psychodrama integrated with CBT + group therapy for 11 sessions for 3 months *v.* control group	RCT	n = 31 (16:15) 19.5 years	BDI	Psychodrama integrated with CBT, and cognitive behavioural group therapy alone, led to reduction in the level of moderate depression
Le *et al.* (2011) United States	Usual care (UC) *v.* 8-week CBT group intervention during pregnancy + three individual sessions *postpartum*	RCT	n = 217 (0:100) 25.5 years	BDI & Mood Screener	Intervention group had significantly lower depressive symptoms and fewer cases of moderate depression at Time 2 than UC group
Medication and psychological combined					
Bastos *et al.* (2013) Brazil	LTPP, Fluoxetine monotherapy or combination for 24 months	RCT	n = 272 (103:169) 29.6 years	BDI & WAIS-III	LTPP and combined treatment seemed to be more efficacious in modifying specific areas of cognition than Fluoxetine alone
Songprakun & McCann (2012*a*) Thailand	Study group received 'The Good Mood Guide: A Self-Help Manual for Depression' *v.* control group	RCT	n = 56 (16:40) 42.1 years	CES-D scale	Between baseline and post-test, a sharp decrease in depression was evident in the intervention group, whereas the level of depression increased in the control group
Songprakun & McCann (2012*b*) Thailand	Intervention group received a self-help manual + standard care and treatment *v.* control group	RCT	n = 56 (16:40) 42.1 years	Kessler Psychological Distress Scale	Lower psychological distress scores in the intervention group than those in the control group

RCT, randomized-controlled trial; BDI, Beck Depression Inventory; HAMD-17, Hamilton Depression Scale; BDI-II, Beck Depression Inventory-II; CES-D, The Center for Epidemiological Studies Depression Scale; LTPP, long-term psychodynamic psychotherapy; WAIS-III, Wechsler Adult Intelligence Scale Version III; CBT-I, cognitive behavioural therapy for insomnia. Details missing in Table 1 is due to such information being unattainable from the studies cited.

[a] Country of origin.

McCann (2012*a*) demonstrated that the inclusion of a self-help manual for depression with usual care (including medication treatment) marginally reduced levels of moderate depression over time. In a further study, Songprakun & McCann (2012*b*) demonstrated the effectiveness of including a self-help manual with usual care in reducing psychological distress in individuals with moderate depression and therefore improving treatment outcomes.

Discussion

In the present systematic review, 14 studies were identified, that were carried out between 2000 and 2014, specifically examining the treatment of moderate depression. Results indicate that psychological therapy on its own has been shown to be effective with this level of severity in depression in a small number of studies. In the present review, there is no evidence to support the effectiveness of antidepressant medication on its own in the treatment of moderate depression. In addition, this review highlights the lack of well-designed studies examining the effective treatments for moderate depression. Only one of the studies under investigation was identified that specifically compared psychotherapy alone with medication alone (i.e. Bastos *et al*. 2013, $n = 272$) and one further study compared psycho therapy with usual care (Le *et al*. 2011, $n = 217$). In both studies, psychological treatment out-performed the medication. Given the limited number of studies in this review, it is argued that this small body of research is not sufficient to inform clinical guidelines and recommendations.

From reviewing the published research, the current review draws attention to the use of classifications of depression such as 'mild to moderate' and 'moderate to severe' within research (e.g. van der Lem *et al*. 2012) and suggests that such classifications, whilst at times clinically useful perhaps, may not be the most useful to inform research. DSM-V is the standard bearer for categorisation but does not categorise the severity of depression using 'mild to moderate' or 'moderate to severe' as bands of depression.

The adherence to clear guidelines for the differential diagnosis of mild, moderate, and severe depression may be necessary in order to more accurately inform treatment guidelines. Large-scale epidemiological studies, such as Wittchen *et al*. (2011), which refer to the gross figures of depression in Europe may in future consider including prevalence rates for the categories of mild, moderate, and severe depression. Gross figures for depression can lead to misinterpretation, due to the varying intervention approaches that may be indicated for the differing levels of severity (see NICE, 2009). This review found that the majority of research investigating depression, typically distinguishes between levels of depression using identification tools such as the HDRS (Hamilton, 1960), BDI (Beck *et al*. 1961), and the General Health Questionnaire (Goldberg & Williams, 1991). Identification tools such as these cannot be the sole measure used to identify a patient's severity or type of depression and the resulting treatment recommendations incorporated. It is also important to take into account the degree of functional impairment and/or disability associated with the possible depression, the duration of the episode, and the clients' own preferences, motivations, intentions, and likelihood of engaging successfully with a treatment modality. In this context, further research needs to conduct studies using diagnostic interviews as a gold standard to identify those with moderate levels of depression. Rather than seeing major depressive disorder as an all-or-nothing condition, it may be more practical and realistic to view it as occurring across a continuum of severity, with DSM categories of mild, moderate, and severe being considered as useful markers/bands or cutoff points for research purposes.

A search of studies from 2000 to 2014 was used in the present study. This resulted in a small number of studies being identified for further review. The decision to only included 'moderate depression' in our search terms in this review was deliberate in order to focus solely on available treatment evidence for moderate depression. Had we adopted a broader approach in our systematic review of studies, incorporating studies on depression other than specifically on moderate depression, it is likely that we would have generated a far larger number of studies for inclusion. This, however, would have defeated the purpose of the study, which was to do a specific review of moderate depression only, resulting in a small number of studies meeting the inclusion criteria. A limitation of this period of research is that it does not include the most recent of studies (i.e. 2014–2017). We would not expect changes in our conclusions from a more up to date review, however, as the results are representative of the historical paucity of research specifically related to 'moderate' depression. Nonetheless, future research studies may follow up on this issue now that it has been highlighted here.

The clinical implication of these findings is that current treatment guidelines for moderate depression, that is 'both an antidepressant and a psychological treatment', may need to be revisited. The treatment of moderate depression needs to be approached with more caution, as this research suggests that there is no evidence for a combined approach for the treatment of moderate depression specifically, as recommended in current guidelines, for example NICE.

In conclusion, given that depression is one of the biggest health challenges the world faces at present

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(The Economist, 2014), we advocate for more research to examine the effectiveness of treatment for different levels/bands of depression severity. Further research may lead to different recommendations for treatment by symptom severity. The present study highlights the urgent need for comprehensive data to be collected on the incidence of and effective treatments, specifically, for moderately depressed people so as to further inform public policy, mental health care strategies, and service delivery. There is currently no funded research that the authors are aware of that is collecting data of this nature in Europe and the present paper hopefully contributes toward encouraging such research to be carried out in future.

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Conflicts of Interest

Dr Declan Aherne, Dr Amanda Fitzgerald, Dr Cian Aherne, Dr Noelle Fitzgerald, Meghan Slattery, and Neal Whelan have no conflicts of interest to disclose.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation with the Helsinki Declaration of 1975, as revised in 2008. The current study is a review paper that does not involve human experimentation. Appropriate ethical standards were upheld throughout whereby research standards were held to the highest quality.

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