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Long title: Psychological treatment of depression and anxiety in patients with co-morbid personality disorder: a scoping study of trial evidence.

Short title: Treatment for depression in co-morbid PD

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Building research capacity in the field of IAPT treatment

Abstract: It is unclear what the best psychological treatment is for depression and anxiety in people with co-morbid personality disorder. Trials of different psychological treatment options for this patient group have been conducted but this evidence has not previously been systematically reviewed or critically appraised. We set out to conduct a scoping review in order to describe which psychological therapies appear most effective in treating depression and/or anxiety in patients with co-morbid personality disorder. PsycINFO, Cochrane library trials, Medline and Embase databases were searched for studies involving randomised, controlled, experimental, parallel-arm comparisons, examining any well-defined, psychotherapeutic intervention for adults, in an outpatient setting, with a clearly defined diagnosis of depression and/or anxiety, and co-morbid personality disorder. 1662 papers were identified. Fifteen met criteria for inclusion and were reviewed. There was weak evidence to support the use of Cognitive Behavioural Therapy (CBT) as a psychological treatment for depression in patients with co-morbid personality disorder. However, the literature is characterised by considerable methodological heterogeneity and further research is needed before there is sufficient evidence to indicate which psychological treatment would be most effective in treating anxiety and/or depression in this patient group.

Keywords: Scoping study, Depression, Anxiety, Personality Disorder, Mental Health, Psychological Therapies

Introduction

Personality disorders are common long-term mental health conditions associated with social disadvantage, poor health and reduced life expectancy (Skodol, Pagano, Bender et al., 2005; Moran, Coffey, Chanen, Degenhardt, Borschmann et al., 2016; Fok, Hayes, Chang, Stewart, Callard et al., 2012). The management of individuals with personality disorder is associated with substantial healthcare costs (Soeteman, Hakkaart-van, Verheul, Busschbach, 2008) and the presence of co-morbid personality pathology is generally associated with a poorer treatment outcome for other health conditions (Newton-Howes, Tyrer, Johnson 2006).

Individuals with personality disorder suffer from high rates of comorbid depression and anxiety (Fribourg, Martinussen, Kaiser, Overgard & Rosenveinge, 2013). However, for the last 60 years, there has been considerable debate about the influence of personality pathology on the treatment of depression and anxiety (Newton-Howes, 2014). The reasons for this debate have stemmed from limited aetiological understanding of personality pathology (Tyrer, 1995), the problematic, complex and changing definitions of personality disorder (Tyrer, Crawford, Mulder, 2011) and arguments over the consanguinity of personality and depressive symptomatology (Mulder, 2002). Under the circumstances, assessing the impact of personality pathology on the treatment of depression and anxiety can be ‘at best confusing and at worst incomprehensible’ (Newton- Howes, 2008, page (106).

Related to this, it is unclear what the best psychological treatment is for depression and anxiety in patients with co-morbid personality pathology (Newton-Howes, 2008, Mulder 2011, Newton-Howes, Tyrer, Johnson, Mulder, Kool, Dekker, & Schoevers, 2014). This is an increasingly important clinical question for mental health services that provide psychological treatments for depression and anxiety under schemes such as the UK's Improving Access to Psychological Therapies (IAPT) (Gyani, Shafran, Layard, Clark 2013). Furthermore, in 2011

the UK government expanded the scope of IAPT services to include the treatment of individuals with personality disorders. Indeed, large numbers of people being seen by IAPT services for depression and anxiety, also have symptoms of personality disorder, and the presence of personality disorder symptoms seems to adversely affect treatment outcomes for those receiving psychological treatment for depression and/or anxiety (Goddard, Wingrove, Moran. 2015). A large divergent literature has emerged in relation to this clinical issue, yet to our knowledge, no study has effectively summarised the evidence base for treating this patient group.

Where the research evidence is divergent, evolving, and its depth and breadth are unknown, a scoping study is considered the most useful and appropriate form of review (Levac, Colquhoun & O'Brien, 2010).

We therefore undertook a scoping review using an established methodological framework developed by Arksey & O'Malley (2005). This framework has been recently enhanced for use by Levac et al., (2010) and reviewed and recommended for use by the Cochrane Public Health Review Group (Armstrong et al., 2011). Using Arksey and O'Malley's framework we reviewed which psychological therapies reduce the severity of depression and/or anxiety in patients with co-morbid personality disorder in an outpatient setting.

Methods

The Arksey and O'Malley (2005) framework includes five key steps: (i) identifying the research question, (ii) identifying relevant studies, (iii) study selection, (iv) charting the data, (v) collating, summarizing and reporting the results. The approach we used is described below according to these five steps.

i. Defining the research question

Which psychological therapies reduce the severity of depression and/or anxiety in patients with co-morbid personality disorder?

ii. Identifying relevant studies

An electronic search strategy was developed by an experienced Cochrane trials search coordinator (SD) in consultation with the research team. In order to maximise the pool of included studies, the inclusion criteria for the search strategy were kept deliberately broad. Pre-designed search filters developed by Cochrane (Lefebvre et al., 2011) were adapted to retrieve randomised controlled trials (RCT) in the areas of 'depression', 'anxiety', 'personality disorder' and 'psychological therapies'. The search strategy was then refined by cross-referencing the search terms, with keywords found in the articles identified via the database search. We also specifically searched for papers written by experts in the field. The following databases were individually searched: Medline, Cochrane Library trials, Medline, PsycINFO and Embase (limited to non-Medline journals) (Appendix A). Searches were de-duplicated. Only papers written in English were reviewed.

iii. Study selection

The following inclusion criteria were used:

Studies published after 1980, involving randomised, controlled, experimental, parallel-arm comparisons examining any well-defined, theory driven, psychotherapeutic intervention for adults (aged 18 years or over) with a diagnosis of depression and/or anxiety, and co-morbid personality disorder.

As the diagnostic criteria for personality disorder, depression and anxiety have changed over time, any study that used standardised and adequately validated measures to meaningfully assess these conditions was eligible for selection. Studies published prior to 1980 were excluded because they preceded the introduction of clear diagnostic criteria for personality disorder.

According to the index of Medical Subject Headings (MeSH), the thesaurus of the US National Library of Medicine's controlled vocabulary, psychotherapy was defined as 'treatment of mental illness or emotional disturbances by verbal or nonverbal communications' (NLM 2009). We included all types of psychotherapy regardless of the theoretical orientation, including psychodynamic therapy, Cognitive behavioural therapy (CBT), systemic therapy or eclectic therapies designed for the treatment of depression and/or anxiety. To maximise the range of information for initial inclusion in the scope, we also included searches for trials on relaxation techniques, patient education programs and musical therapies. However, no such studies were found. We pragmatically only included treatments delivered in a community/outpatient setting, as this is the setting in which most care is currently delivered. Eligible comparator interventions included any specific psychotherapeutic intervention, as described above or unspecific control interventions, including clinical management, standard care, treatment as usual, waiting list or drug treatment.

All outcomes were either self-rated or interviewer-assessed using standardised, adequately validated measures. Primary outcomes described were depression and/or anxiety severity measured using validated clinical measures.

The final studies included in the review were selected as a result of iterative discussion and a series of consensus meetings between three of the four authors (LF, KT and PM). LF led the selection process. In the interests of optimising the range of studies for inclusions, we did not initially place strict limitations on the search terms, identification of studies, or study selection. As we became more familiar with the research literature, we re-defined our search terms and undertook more selective searches. Early in the review process, we decided to exclude observational as well as qualitative studies. We did this because our research question was principally concerned with the effectiveness of treatment and we concluded that randomised controlled trials (when well conducted) provided the only unbiased assessment of likely effectiveness. We also decided to narrow the scoping review to studies that had one of the following aims:

- 1) Comparison of the efficacy of psychological interventions for depression and/or anxiety in patients with co-morbid personality disorder
- 2) Comparison of the efficacy of psychological interventions for patients with personality disorder in which baseline and outcome measures for depression and/or anxiety had also been reported
- 3) Investigation of the impact of personality disorder on the treatment of depression and/or anxiety.

LF and PM co-rated a 1% sample of the 1662 abstracts in order to check the reliability of our final selection process. We agreed in the case of 75% of abstracts and in the remaining 25%,

the source of disagreement related to whether to include studies that aimed to investigate the impact of personality disorder on the treatment of depression and/or anxiety. After discussion, we resolved to include this last category of studies because although these studies did not directly tackle the question of effectiveness, we considered that they provided potentially valuable information regarding the comparative effectiveness of psychological treatments for depression and /or anxiety, in the presence of personality disorder. We subsequently reached 100% consensus on the 1% sample.

iv. Charting the data

A spreadsheet in Word was created to chart the following data extracted from relevant studies: study title, authors, year of publication, study location, intervention type, study population, study aims, methods, primary outcome measures, secondary outcome measures, results, conclusion. These data were independently selected by LF and PM for the 15 studies included in the review to check that data extraction would be consistent.

v. Possible meta-analysis of findings

As this was a scoping review and our aim was simply to map the relevant literature relating to effectiveness of treatment in this population, we did not adopt any a priori criteria to decide if a meta-analysis should occur. Notwithstanding, the final pool of 15 studies included a mix of comparisons of different treatments with different comparators and it would have been inappropriate to combine all the studies (or a subgroup thereof) in a single meta-analysis (Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]).

Results

The initial literature scope produced 1662 potential papers. After having read the abstracts of these papers, 1596 papers were rejected because they did not meet the inclusion criteria. Sixty-six papers were then retrieved and the full text was read. Following this process, a further 51 papers were subsequently rejected as they did not meet the inclusion criteria. Fifteen studies, containing 2011 participants, were included in the final scope (Figure 1).

Characteristics of the included studies

The characteristics of the final 15 studies are summarised in Table 1. These studies were published between 1991 and 2014; five studies were from North America, three from the Netherlands, two from Canada, two from New Zealand, one from Spain, one from Germany and one from Iran. The most commonly used measures of recovery from depression were: Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960), Hamilton Rating Scale for Depression (HAM-D) (Jonghe, 1994), Beck Depression Inventory (BDI) (Beck, Ward, Mendelson, Mock & Erbaugh, 1961) and Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). The Hamilton Anxiety Rating Scale (HARS) (Hamilton, 1959) and State Trait Anxiety Inventory (STAI) (Martean & Bekker, 1992) were the most commonly used measures of recovery from anxiety. The Structured Clinical Interview (SCID-II) (First, Gibbon, Spitzer, & Benjamin, 1997) was typically used to diagnose personality disorder in the study samples.

All the studies focused on the treatment of depression. Five studies also considered the treatment of anxiety.

With the exception of a single study using a three-arm treatment comparison (Bamelis, Evers, Spinhoven, & Arntz, 2014) all of the studies used a two-arm approach to compare the

efficacy of various psychological treatments. Five studies compared psychological therapies head-to-head, of which four compared Interpersonal Therapy (IPT) with Cognitive Therapy or Cognitive Behavioural Therapy (CT/CBT). Four studies compared psychological therapies with treatment as usual TAU (described as either naturalistic pharmacological treatment and/or an unspecified therapy), and six studies compared psychological therapies with pharmacotherapy.

Psychological therapies included in studies

A wide range of psychological therapies were explored, including: Short Psychodynamic Supportive Psychotherapy (SPSP) (n=1), Transference-Focused Psychotherapy (TFP) (n=1), Clarification-Orientated Psychotherapy (n=1), Cognitive Behavioural Therapy (CBT) (n=2) and its derivative forms; Cognitive Therapy (CT) (n=4), Behavioural Activation (BA) (n=1), Dialectic Behavioural Therapy (DBT) (n=1), DBT Skills Training (n=1), Schema Therapy (ST) (n=2) and Cognitive Behavioural Analysis System Psychotherapy (n=1) and lastly Interpersonal Therapy (IPT) (n=5) and Psychoeducation (n=1).

Studies comparing psychological therapies head-to-head

Five studies directly compared two psychological treatments, of which four compared IPT with CT or CBT: The smallest of these studies, had only 28 participants, raising questions about its internal validity (Bellino, Zizza, Rinaldi & Bogetto, 2007). However, two larger studies using 160 participants in total (Carter, Luty, McKenzie, Mulder, Frampton & Joyce, 2011) and 75 participants in total (Joyce, McKenzie, Carter, Rae, Luty, Frampton & Mulder, 2007), concluded that CT/CBT was a more effective treatment than IPT for treating depression in people with depression and co-morbid personality disorder.

A further study investigating the impact of personality disorder subtype on the treatment of depression, found CT to be more effective at reducing depression in individuals with avoidant personality disorder and IPT more effective in reducing depression in individuals with obsessional compulsive personality disorder (Barber & Muenz, 1996).

The fifth study in this group compared CBT with ST (Carter, McIntosh, Jordan, Porter, Frampton & Joyce, 2013). While this study reported that both treatments improved depressive symptomology, both treatments appeared equivalent in effect. Again, however, the robustness of these findings is questionable as the study relied on a sample of only 55 participants, with limited power to detect group differences in treatment outcomes.

Studies comparing psychological therapies with treatment as usual (TAU).

Four studies compared specific psychological therapies with TAU. No study compared the same treatment, and the TAU control groups in the studies were very widely defined, ranging from 'naturalistic pharmacotherapy' to any unspecified psychotherapy (Table 1). The efficacy of five treatments to reduce depressive and anxious symptomology was tested in these studies and included: Psychoeducation (Colom, Vieta, Sánchez-Moreno, Martínez-Arán, Torrent, Reinares & Comes, 2004), DBT (Lineham, Armstrong, Suarez, Allmon & Heard 1991), TFP (Doering, Hörz, Rentrop, Fischer-Kern, Schuster, Benecke, & Buchheim, 2010) and as part of a three-arm treatment comparison, ST and Clarification-Orientated Therapy (Bamelis et al., 2014). One of the four studies by Doering et al., (2010) found TFT to be no better or worse than TAU. However, Lineham et al (1991) found those in the treatment group receiving DBT had fewer in-patient stays. Bamelis et al., (2014) found patients treated for depression with Schema Therapy had fewer depressive episodes at 36-month follow-up than those receiving Clarification-Orientated Therapy or any other undefined psychotherapy. Colum et al., (2004) reported statistically significant superiority of

the Psychoeducation over unspecified TAU on the criterion of recurrence of depressive symptoms at 2-year follow-up.

Pharmacotherapy versus psychological treatments

Six studies compared the efficacy of psychological treatments versus pharmacotherapy for depressive symptoms in patients with co-morbid personality disorder. Four of these studies compared combined therapy (drug treatment + a psychological treatment) with mono-therapy (drug treatment). One large trial, with 681 participants, focused on patients with cluster C personality disorders and found no difference in treatment outcome between mono-therapy and combined therapy using a form of cognitive behavioural therapy (Maddux, Riso, Klein, Markowitz, Rothbaum, Arnow, & Thase 2009). The remaining three trials all found combined therapy to be more effective at reducing depressive symptoms than mono-therapy. Therapies under examination were SPSP (Kool, Dekker, Duijsens, de Jonghe & Puite 2003), DBT skills training (Lynch, Cheavens, Cukrowicz, Thorp, Bronner & Beyer 2007) and IPT (Bellino, Zizza, Rinaldi & Bogetto 2006).

The remaining two studies that compared pharmacotherapy directly with a psychological treatment, found BA to be more effective than pharmacotherapy (Moradaveisi, Huibers, Renner, Arasteh, & Arntz, 2013) and CT to be less effective than pharmacotherapy (Fournier, DeRubeis, Shelton, Gallop, Amsterdam, & Hollon 2008).

Discussion

This scoping review confirms that the body of knowledge supporting the psychological treatment of depression and/or anxiety in people with personality disorder is both slender and highly heterogeneous. The use of multiple psychological therapies, small sample sizes, differing follow-up periods and a wide range of primary outcome measures (Bateman,

Gunderson & Mulder, 2015) makes drawing any firm conclusions extremely difficult. The short duration of follow-up (the average follow-up time being 6 months) is particularly problematic, as in order for treatments to be deemed effective, they need to have a sustained effect on core symptoms of the disorder.

Only four studies explored treatments for anxiety in personality disordered patients (Bellino et al., 2006, 2007; Doering et al., 2010 and Bamelis et al., 2014), of which only two found symptoms of anxiety to improve with treatment (Doering et al., 2010, Bamelis et al., 2014) and one found CT more effective than IPT in the reduction of anxiety symptoms. On the basis of such scant evidence, we conclude that it is not currently possible to determine which psychological treatment is preferable for the treatment of anxiety in people with personality disorder. These findings highlight the pressing need for further research in this area.

The strongest evidence base that we could identify related to the use of CT or CBT for depression: seven of the 15 studies reviewed in this paper found it to reduce depressive symptoms in people with personality disorder (Barber et al 1996, Bellino et al., 2007, Carter et al., 2011, Carter et al., 2013, Fournier et al., 2008, Joyce et al., 2007 and Maddux et al., 2009) - three of which found it to be superior to another treatment (Barber et al., 1996, Carter et al., 2011 and Joyce et al., 2007) most typically IPT. However, caution needs to be exercised when interpreting these findings. The majority of identified studies did not assess for the treatment of the underlying personality disorder as well as the depression and anxiety, thus ignoring the possibility that personality disorder, depression and anxiety may be consanguineous rather than truly co-morbid conditions (Tyrer & Johnson, 1996, Mulder, 2002). Indeed, it could be argued, that unless the underlying personality disorder is treated, one would not expect to see any improvement in apparent 'epiphenomena' such as depression or anxiety (Bateman and Fonagy, 2015).

Our initial literature searches, not included in this scoping review, highlighted a growing body of non-RCT literature in the field. Such studies included investigations into the effect of CBT focusing on early core beliefs (Keefe, Webb & ReRubeis, 2016), emotional intelligence training (Jahangard, Haghghi, Bajoghli, Ahmadpanah et al., 2012), mentalization-based therapy (Bateman & Fonagy, 2016) and radically open dialectical behaviour therapy (Lynch, Whalley, Hempel, Byford, Clarke et al., 2015). Indeed, pilot studies for radically open dialectical behaviour therapy indicate that this treatment is a feasible, option for the treatment of depression and anxiety in patients with specific types of personality disorder (Lynch et al 2003, Lynch et al 2007), notably paranoid, avoidant and obsessive-compulsive personality types. (Candrian, Schwartz, Farabaugh, Perlis, Ehlert et al., 2008; Fava, Farabaugh, Sickinger, Wright, Alpert et al., 2002; Lynch, Whalley, Hempel, Byford, Clarke et al., 2015). This emerging research highlights the importance of considering the patient's underlying personality disorder when treating depression and/or anxiety and suggests that, the treatment of depression and anxiety in those with personality disorder might potentially be optimised, by stratifying treatment on the basis of personality disorder symptom profile. Yet this is not a simple task (Stiles, Shapiro, & Elliot, 1986) and we require a better understanding of how to do this both effectively and efficiently.

Conclusion

Variation in the quality and scope of studies limits our knowledge about the best way to treat depression and/or anxiety in people with personality disorder. Whilst we found some support for CT or CBT, the data from these studies could not be pooled due to the wide range of comparator treatments and measurement tools used, as well as the varying time-points reported. There is a pressing need for adequately powered, methodologically robust RCTs to test the effectiveness and cost-effectiveness of psychological treatments for depression and/or

anxiety in patients with personality disorder. Further research will also help us to understand whether adaptations need to be made to existing psychological treatments for depression, so that these treatments are more effective for people with personality disorder.

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