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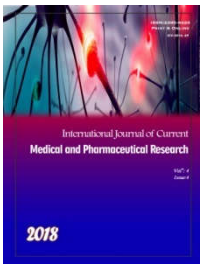

SYSTEMATIC REVIEW OF THE EFFICACY OF PHARMACOLOGICAL TREATMENT ALONE VS. PSYCHOTHERAPY ALONE OR THE COMBINATION OF BOTH IN THE TREATMENT OF DEPRESSIVE DISORDERS

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ABSTRACT

Depression is a challenging condition to treat especially where the efficacy of the current types of treatments has been in debate for decades. The aim of this review was to compare the effectiveness of medications to psychotherapy interventions and the combination of both interventions in the treatment of depression. This was conducted by evaluating the evidence from studies that investigated the efficacy of alone interventions and dual therapy to identify the best course of treatment for depression. Twenty studies were selected of which ten were directly compared pharmacotherapy with psychotherapy and a further ten compared the combination of both to either of the two monotherapies. The results showed that in either of monotherapies cohorts, the rates of response, remission and changes in symptom severity were near equivalent for both but dropout rates were higher for the medications groups. Comparing dual therapy to the monotherapies showed higher efficacy in terms of response, remission and reduction of symptom severity for combination. The difference however seen less with pharmacotherapy and showed psychotherapy being least effective but the difference was in efficacy is small in the majority of the studies, to a point in which the question of'is the difference clinically significant' remained unanswered which require more definitive future research.

INTRODUCTION

Depression is a prevalent mental health disorder, which is also one of the top causes of disability worldwide. Estimates of over 300 million people are affected by depression worldwide with women being the most affected when compared to men(World Health Organization, 2017). According to the Chief medical officer in the United Kingdom (UK) annual report in 2013 approximately 70 million sick days are accounted for due to mental illness which costs the UK economy between 70-100 billion pounds each year (Department of Health, 2014). In the 2013 UK Wellbeing Survey, nearly 1 in 5 people in the UK aged 16 and older showed symptoms of anxiety or depression. This percentage was higher for females (21.5%) than for males (14.8%), (Mentalhealth.org.uk, 2015).The evidence found shows that depression does not just affect a certain population as all ages and genders are affected by this crippling condition. However, depression prevalence is as high as 2 in 5 in older people living in care homes in the UK (Rcpsych.ac.uk, 2017). As a rule, psychotic diseases require pharmacological intervention as first line treatment with psychotherapy's usefulness not exceeding an adjunct role, conversely in depression; psychotherapy provides an alternative first line treatment. The preferred treatment method usually dependent upon: treatment availability, previous history of response, patient preference and ability to comply with selected method (Bennett and Brown, 2003).

In the 20th century Kraeplin identified the different causes of depression as being 'endogenous' and 'exogenous' (Sanders and Hill, 2014). This fundamental understanding helped in paving the way to more modern approaches to define depression. Kraeplin also introduced opium in the form of a tincture as treatment of melancholia or sadness. Modern medicines only started to peak after the 1950's when antidepressants such as chlorpromazine were introduced. Opium use for depression was left behind after introduction of imipramine (Ban, 2002).

The current knowledge for the pathophysiology of depression is conflicting, debatable and does not agree on a "unified hypothesis"(Hasler, 2010). This conflict is due to the fact that numerous theories are thought to be the trigger for depression but may not fully explain the aetiology of the disease. Genetic influence plays an undeniable role of the aetiology of depression (Brigitta, 2002). On a cellular level the alterations of serotonergic neuronal function in the CNS was recognised in patients diagnosed with depression (Owens, 1994). The observation of reduced platelet and brain serotonin transporter binding isbelieved to be consistent in patients diagnosed with

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depression during the period of low mood. One of the most accepted theory's is the 'monoamine-deficiency' hypothesis; which is explained by the inhibition of monoamine oxidase inducing a larger availability of monoamines in presynaptic neurones thus providing an antidepressant effect. This led to the belief that the depletion of neurotransmitters such as serotonin, dopamine or norepinephrine leads to depression (Hasler, 2010).

There are a number of different types of antidepressant treatments available in the UK including selective serotonin reuptake inhibitors (SSRI), serotonin-noradrenaline reuptake inhibitors (SNRI) and tricyclic antidepressants (TCA) (NHS.UK, 2015). Cognitive behavioural therapy (CBT) can also be used as alternatives toor as a combination with antidepressants. According to NICE guidelines the number of CBT sessions can be classed as a low or high-intensity psychosocial intervention depending on how severe the patient symptoms are, e.g., for high intensity the number of sessions usually continue for up to 3-4 months and up to 16-20 sessions (Nice, 2016).

The use of antidepressants reached its highest as the number of antidepressant items dispensed more than doubled in 10 years, were 64.7 million antidepressant items dispensed in 2016 compared to 31.0 million dispensed in 2006 (Digital.NHS.uk, 2017). NICE guidelines state that the use of psychotherapy or pharmacotherapy for depression is warranted and may be used depending on the severity of depression and the patient personal preference (NICE, 2016).

A meta-analysis (Cuijpers *et al*., 2013) which compared the efficacy of mono-intervention of psychotherapy or pharmacotherapy stated that the difference in effects between the two was 'small to non-existent'. Although it further states that different forms of both therapies have 'varying degrees of efficacy' in treating depression for example TCAs were less effective than psychotherapy and non-directive counselling was seen less efficacious than pharmacotherapy in general (Cuijpers *et al*., 2013). In another meta-analysis, both mono-interventions (Leichsenring *et al*., 2016) were deemed to be equivalent in short term with more long-term benefit seen with psychotherapy. It further regards the limitations to response and remission in both interventions as a clear need for a more improved form of treatment. There seems to be a varying degree of agreeability in which intervention is better. A meta-analysis (Kamenov *et al*., 2016) compared all three interventions showed that combination therapy is superior, however monotherapy with either intervention shown to be effective for improving function and QOL. Another study (Hollon *et al*., 2005) further clarifies that both mono-intervention are effective but combination treatment may further enhance the likelihood of response over either monotherapy especially in severe depression.

To assess depression, a depression rating scale is needed which is a useful way to determine patients level of depression before and after treatment to identify its success and effectiveness. It usually takes 15 minutes depending on the scale such as Hamilton Rating Scale for Depression (HRSD/HAM-D). Questions include feelings of guilt, presence of insomnia, displaying anxiety and/or somatic symptoms. Other forms of scales include Becks Depression Inventory, Montgomery-Åsberg Depression Rating Scale (ADRS) and Children's Depression Rating Scale-revised total score (CDRS) (Cusin *et al*., 2009).

This systematic review will explore available evidence and compare the efficacy of various psychotherapeutic interventions with pharmacological intervention and their combination.

The aim of this systematic review is to assess the effectiveness of antidepressant drugs in comparison to psychotherapy or a combination of both using randomised controlled trials where the efficacy of individual or combined therapies is the primary outcome.

Methods and Design

For the identification of trials comparing pharmacotherapy with psychotherapy or the combination of the two, three databases (PubMed, CENTRAL and Science Direct) were searched. The search strategy included the following keywords: Pharmacotherapy OR psychotherapy OR combination AND depression AND efficacy.

Three hundred and eighty two trials were found in PUBMED, 296 trials found in Cochrane Library and 2 trials found in Science direct databases (n=680). After reading the abstract 660 papers were excluded as a result of either the abstract did not have relevant information to depression or free full text was not available, leaving 20 randomised controlled trials (RCT) which fit the inclusion criteria, with total of 3673 patients.

Tools used included the HRSD (n=16), Beck Depression Inventory (BDI) (n=1), CDRS revised total score (n=1) and Montgomery-Åsberg Depression Rating Scale (MADRS) (n=1). Response and remission was recorded in some RCTs.

Inclusion criteria: RCTs which 1) compared either psychotherapy intervention against any active pharmacological intervention OR the combination of both in the treatment of 2) depression 3) as the primary outcome of interest being the efficacy of the intervention (reduction in the depression symptoms severity) and participant's attrition rate.

For the purpose of this systematic review efficacy is defined as the response to treatment and reaching remission.

Exclusion criteria: Current or past diagnosis of schizophrenia or other psychotic disorders; diagnosis of alcohol or drug abuse or dependence (except nicotine) or anorexia in the past year; psychotic symptoms, acute suicidal risks or the use of interventions such as ECT and cortical stimulation The Cochrane Bias risk tool was used to assess the validity and accuracy of the studies in terms of fairness and conducted appropriately (Methods.cochrane.org, 2017)

Data extraction

Outcomes of this study were assessed either as dichotomous variables (the proportion of patients who report improvement of depression symptoms, achieve remission and dropouts) or as continuous variables (depression severity scales).

The primary outcome for this review was the efficacy of the used therapy described as the difference in mean depressive symptoms, as the included studies evaluated treatment efficacy on a wide range of scales.

FINDINGS AND DISCUSSION

The most commonly studied interventions were antidepressants, CBT or IPT. Firstly the efficacy of pharmacotherapy alone compared to the efficacy of

psychotherapy alone was compared, then the two mono-therapies were compared to the combination of pharmacotherapy and psychotherapy.

Psychotherapy vs. Pharmacotherapy

Ten RCTs were used to compare the efficacy of pharmacotherapy to that of psychotherapeutic treatment modalities. There were a total of 1602 patients included, of which 35.4% were male and included patients from the age of 18 and above. The majority of the diagnosis was major depressive disorder (MDD) and the rest were dysthymia, Postpartum Depression (PPD), Treatment Refractory Depression (TRD) and atypical depression (Table 1). All studies used HDRS as a depression rating score apart from one (Leff *et al*.2000) which used BDI.

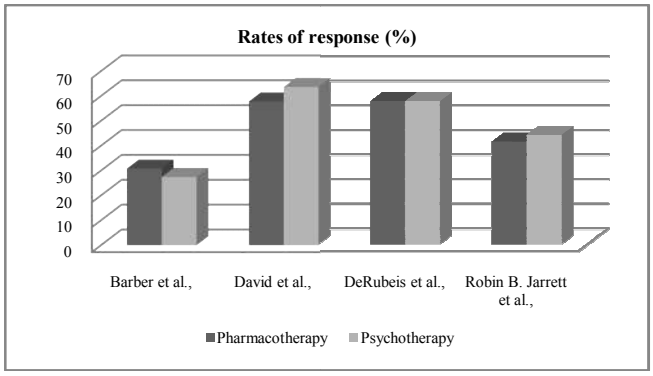

Figure 1 The average rates of response for psychotherapy and pharmacotherapy

Table1: Comparative analysis, efficacy of pharmacotherapy vs. psychotherapy

Study	Numberof patients	Intervention	DRS baseline	DRS Post-treatment	Change in DRS	Response (%)	Remission (%)	Dropouts (%)
(Barber *et al*., 2011)	156 (MDD)	SET (Psychotherapy)	19.9	14.5	-5.4	27.5	21.6	23.5
		Sertraline (Pharmacotherapy)	19.0	14.2	-4.8	30.9	25.5	40
(Elkin *et al*., 1989)	250 (MDD)	IPT (Psychotherapy)	18.9	6.9	-12	/	43	23
		CBT (Psychotherapy)	19.2	7.6	-11.6	/	36	32
		Imipramine (Pharmacotherapy)	19.2	7.0	-12.2	/	42	33
(Leff *et al*., 2000)	77 (MDD with a critical partner)	Couples therapy (Psychotherapy)	25.4 (BDI)	9.0	-16.4	/	/	15
		Desipramine (Pharmacotherapy)	28.1 (BDI)	21.0	-7.1	/	/	56.8
(David *et al*., 2008)	170 (MDD)	REBT (Psychotherapy)	23.1	8.8	-14.3	64.9	43.9	9
		CT (Psychotherapy)	22.9	8.6	-14.3	62.5	50	10
		Fluoxetine (Pharmacotherapy)	21.4	8.8	-12.6	57.9	47.4	14
(Röhricht *et al*., 2013)	31 (Chronic depression)	Group BPT (Psychotherapy)	28.2	20.9	-7.3	/	/	31.3
		TAU (Pharmacotherapy)	27.2	29.5	+2.3	/	/	33.3
(DeRubeis *et al*., 2005)	240 (MDD)	CT (Psychotherapy)	23.5	10.2	-13.3	58	40	15
		Paroxetine (Pharmacotherapy)	23	9.7	-13.3	58	46	16
(Zlotnick, 2008)	162 (PPD)	IPT (Psychotherapy)	22.0	8.2	-13.8	/	/	19
		Sertraline (Pharmacotherapy)	21.8	8.1	-13.7	/	/	32
(Jarrett *et al*., 1999)	108 (atypical MDD)	Acute phase CT (Psychotherapy)	21.11	10.25	-10.86	44.4	/	14
		Phenelzine (Pharmacotherapy)	20.03	8.64	-11.39	41.6	/	25
(Miranda *et al*., 2006)	267 (MDD)	Group/individual CBT (Psychotherapy)	16.28	-7.1	-9.18	/	/	64.5
		Paroxetine (Pharmacotherapy)	17.95	-5.1	-12.85	/	/	53
(Dekker *et al*., 2008)	141 (MDD)	SPSP (Psychotherapy)	20.4	18.39	-2.01	/	/	22.7
		Venlafaxine (Pharmacotherapy)	19.8	15.59	-4.21	/	/	32.2

Rates of Response

There were four studies that recorded response involving the mono therapies which was defined as a HDRS score of 12 and lower or a 50% reduction HDRS score. Not every study made this aspect as an outcome which made the available data analysed limited, however from those studies which were analysed, the rate of response for both psychotherapy alone and pharmacology alone was similar with one of the studies having identical rates of response at 58% (DeRubeis *et al.,* 2005). Rates of response can be linked to efficacy as it is a good sign of how effective the intervention is on patients. For studies which included more than one type of psychotherapy, the average mean was calculated and that result became the final result for figure 1 graph. The average rate of response for psychotherapy is 48.4% of the targeted population, which is of a similar value to pharmacotherapies mean rate of response of 47.1%. The near equal rates of response can prove the efficacy of both interventions and the equivalence of them both.

Rates of Remission

Four studies were included in this analysis where remission was reported as primary outcome measures and from this we can see the results on the bar graph at figure 2. Similarly, there was no significant difference was calculated for remission, displaying a near equal efficacy. The mean number of patients achieved remission was 40.99% for psychotherapy and 42.36% for pharmacotherapy respectively.

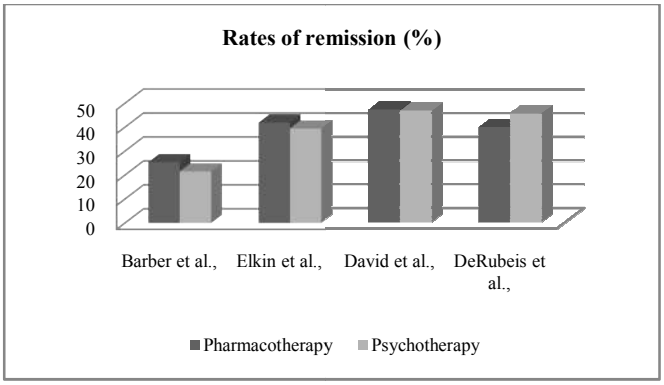

Figure 2 Rates of Remission for psychotherapy and pharmacotherapy

Changes in depression scale

Apart from Rohrichta *et al*.,(2013) the rest of the studies showed decreased depression severity regardless of the type of the intervention. The biggest decrease in depression severity was in Leff *et al*., (2000) in which the patients on average had symptoms reduction score of 16.4 in the psychotherapy treatment group on the DRS scores compared to a reduction of symptoms of 7.1 in pharmacotherapy treatment group. Coincidentally it was the only study that used BDI instead of HDRS.

Rohrichta *et al*., (2013) reported that pharmacotherapy alone increased the severity of depression (+2.3 from baseline), the only study to have this finding.

The other eight studies had more similarity in the level of reduction in symptoms which was insignificant for all interventions (Figure 3). Total average mean change in depression severity for psychotherapy was a decrease of 10.4 and pharmacotherapy had a mean reduction by nine on the scale (difference of 1.4).

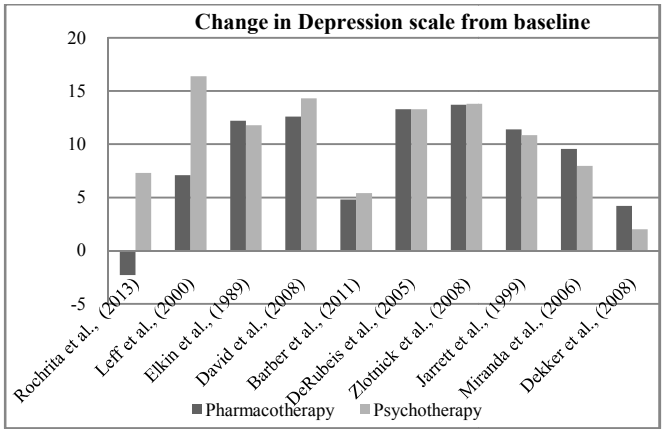

Figure 3 Reduction in the depression symptoms for psychotherapy and pharmacotherapy

Dropout Rate

Figure 4 shows the dropout rate for the ten studies comparing pharmacotherapy with psychotherapy. From this graph we can see that nine out of the ten studies show that the dropout rate for pharmacotherapy was higher than psychotherapy. The biggest difference in dropout rate difference is Leff *et al*., (2000) where 56.8% of patients taking desipramine dropped out compared to 15% withdrawing from psychotherapy.

The most common reason for dropout in pharmacotherapy was side effects and the toll it was having on patients. Miranda *et Al*., (2006) was the only RCT in which more patients from the psychotherapeutic intervention dropped out (64.5% vs 53%).

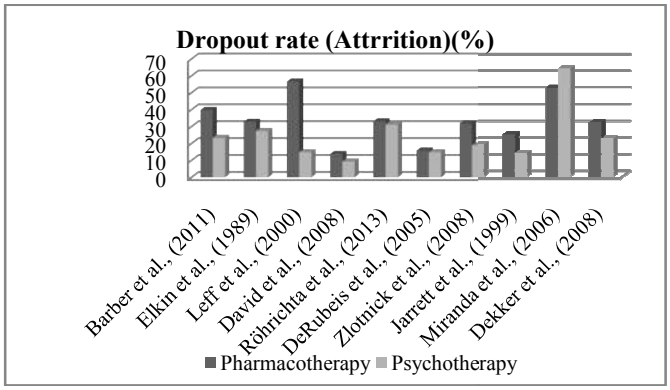

Figure 4 Dropout rate for the ten studies comparing pharmacotherapy with psychotherapy

The calculated mean score of dropout rates for psychotherapy are 24.2% which is roughly a quarter of patients treated. The average number of patients to dropout for pharmacotherapy was 33.53% or one in three patients.

Combination Therapy vs. Monotherapies

Ten RCTs were included in the findings of the efficacy of the combination of pharmacotherapy and psychological interventions compared with that of monotherapy of either intervention. A total of 2071 patients aged 11 and above were included in this analysis with the majority of the diagnoses being MDD, TRD and dysthymia. Some studies did not include response and/or remission as an outcome and therefore were not included the data analysis. Also, most studies used HDRS as a measurement of severity apart from three, two used CDRS-Rt and one used MADRS.

Rates of Response

On figure 5, there seems to be a trend where combination achieves higher response rates than either intervention alone; all apart from Markowitz *et al*., (2005) and Goodyer *et al*., (2007), which has near equal rates of response for both pharmacotherapy alone and combination (58.3% vs 57.1% and 39.4% vs 33.7% respectively).

Studies with psychotherapy alone as an intervention showed a significant difference in percentage of patients that have responded to the treatment compared to combination: Keller *et al.,* (2000) recorded as 48% vs 73%, Glass *et al*., (2005) recorded as 43.2% vs 71% and Markowitz *etal*., (2005)recorded as 32.9% vs 57.1% favouring combination. Pharmacotherapy has shown in three studies to have near equal or higher rates of response to combination therapy: Goodyer *et al.,* (2007) reported 39.4% vs 33.7% and Markowitz *et al*., (2005) reported 58.3% vs 57.1%,Lam *et al*., (2013) reported 61% vs 63%, however the rest of the studies showed that combination was significantly superior to pharmacotherapy alone: Keller *et al*., (2000) reported 48% vs 73%, Schramm *et al*., (2007) reported 51% vs 70%, Souza *et al*., (2016)reported 22.2% vs 35.5% and Glass *et al*., (2005) reported 60.6% vs 71%. Three studies compared all three interventions together; (Keller et al., (2000); Glass *et al*., (2005) and Markowitz *etal*., (2005)), using these studies to compare efficacies shows that the mean rate of response for psychotherapy was 41.36% whilst pharmacotherapy was 55.63%. However the intervention that proved most effective was combination therapy with 67.03%. Combining all studies, the averages can be shown from figure 5. Psychotherapy still has a mean rate of response of 41.36% as the other studies did not include data for this. For pharmacotherapy and combination, a further four studies were found matching the response rate. Considering the previous three studies mentioned the mean rate of response for pharmacotherapy was 48.64% and 57.61% for combination therapy.

Table 2 Combination vs. either intervention

Study	number of patients	Intervention	DRS (baseline)	DRS Post treatment	Change in DRS	Response (%)	Remission (%)	Dropouts (%)
(Keller *et al*., 2000)	681 (chronic MDD)	Cognitive behavioural analysis (Psychotherapy)	26.4	15.1	-11.3	48	33	25.5
		Nefazodone (Pharmacotherapy)	26.8	14.7	-12.1	48	29	26.8
		Combination	27.4	9.7	-17.7	73	48	21.2
(Schramm *et al*., 2007)	124 (MDD)	Sertraline (Pharmacotherapy)	21.9	11.8	-10.1	51	34	14.8
		Combination (+ IPT)	25.1	8.9	-16.2	70	49	15.9
(Goodyer *et al*., 2007)	208 (MDD)	Fluoxetine (Pharmacotherapy)	75.3 (CDRS-Rt)	61.0	-14.3	39.4	21.3	12.6
		Combination(+CBT)	75.1 (CDRS-Rt)	62.8	-12.3	33.7	19.4	17.1
(Glass, 2005)	439 (MDD)	CBT (Psychotherapy)	59.64 (CDRS-Rt)	42.06	-17.58	43.2	/	21.63
		Fluoxetine (Pharmacotherapy	58.94 (CDRS-Rt)	36.30	-22.64	60.6	/	16.5
		Combination	60.79 (CDRS-Rt)	33.79	-27	71	/	14
(Chaput *et al*. 2008)	22 (MDD, TRD)	CBT (Psychotherapy)	22.4	15	-7.4	/	/	54.5
		Combination (+ Quetiapine)	23.4	16	-7.4	/	/	9.0
(De Jonghe *et al*., 2001)	167 (MDD)	Fluoxetine (Pharmacotherapy)	21	13.9	-7.1	/	15.5	40
		Combination(+SPSP)	20	11.1	-8.9	/	37.3	32
(Markowitz *et al*., 2005)	94 Dysthymia	IPT (Psychotherapy)	18.9	12.5	-6.4	34.8	33.3	17.4
		BSP (Psychotherapy)	19.7	13.6	-6.1	31.0	33.3	42.3
		Sertraline (Pharmacotherapy)	17.8	8.3	-9.5	58.3	37.5	20.8
		Combination(Sertraline + IPT)	19.7	9.9	-9.8	57.1	52.9	19.0
(Souza *et al*., 2016)	40 (MDD/ TRD)	TAU (Pharmacotherapy)	18.45	13.9	-4.55	22.2	16.7	21.7
		Combination (TAU + IPT)	19.8	14.0	-5.8	35.5	28.6	5.9
(De Jonghe *et al*., 2004)	191 (MDD)	SPSP (Psychotherapy)	18.14	11.35	-6.79	/	32.1	25
		Combination (+ Venflaxine)	17.99	9.35	-8.64	/	42.4	35
(Lam *et al*., 2013)	105 (MDD)	Escitalopram (Pharmacotherapy)	27.1 (MADRS)	12.8	-14.3	61	53	9.8
		Combination (+ telephone CBT)	28.2 (MADRS)	12.5	-15.7	63	56	16.6

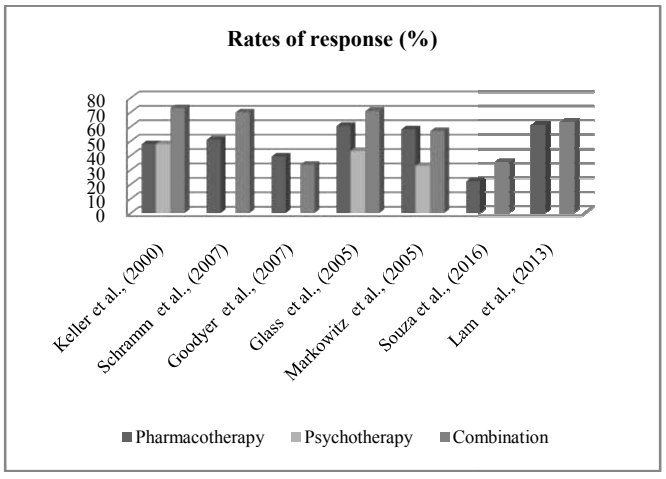

Figure 5 Rate of response, combination vs. either intervention

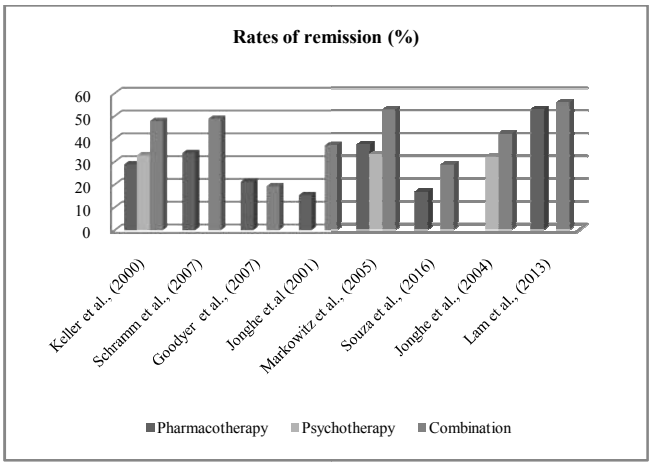

Figure 6 Rates of Remission, combination vs. either intervention

Rates of Remission

The rates of remission are shown on figure 6. Combination therapy has the highest rate of remission in seven of the eight studies that recorded remission, the only study did not agree with this finding was Goodyer *et al*., (year) which reported 21.3% vs 19.4%, in which the rates of remission were near equal but slightly higher for pharmacotherapy.

The remission rates for all psychotherapy interventions recorded were all very similar; 33% in Keller *et al*., (2000), 33.3% in Markowitz *et al*., (2005) and 32.1% in Jonghe *et al*., (2004) with a mean of 32.8% of patients receiving treatment recovered.

Two studies recorded the remission rates for all three interventions together; Keller *et al*., (2000) and Markowitz *et al*., (2005). The mean rates of recovery were 33.15% for psychotherapy, 33.25% for pharmacotherapy and 50.45% for combination treatment.

Changes in depression scale

In every study apart from Goodyer *et al*., (2007) combination therapy caused a greater decrease in depression severity. However, the difference isn't significantly greater than the other interventions apart from three studies; difference of 6.1in Schramm *et al*., (2007), 6.4 /5.6 in Keller *et al*., (2000) and 9.42 / 4.36 in Glass *et al*., (2005). Goodyer *et al*., (2007), Lam *et al*., (2013) and Glass *et al*., (2005) used a different DRS from majority.

The mean change from baseline was calculated using the three studies (Keller *et al*., (2000), Glass *et al*., (2005) & Markowitz *et al*., (2005)) which included all three interventions. An average decrease of 11.71 in terms of DRS for psychotherapy compared to a decrease of 14.75 for medication showing comparable outcomes but favouring pharmacotherapy. The mean reduction for combination supersedes both monotherapy interventions with a reduction of 17.97 highlighting its superiority to either therapies alone.

Five studies compared pharmacotherapy alone with combination, pharmacotherapy produced an average reduction of 10.06 through the five studies (-7.1,-4.5,-14.3,-10.1,-14.3) whereas combination managed to reduce the severity by 11.78 (-8.9,-5.8,-15.7,-16.2,-12.3). Psychotherapy interventions directly compared to combination therapy were limited to two studies. A mean reduction of 7.095 for psychotherapy (-6.79,-7.4) and for combination therapy 8.02 (-8.64,-7.4 respectively) showed that combination therapy is slightly favoured to reduce more than mono therapy interventions (Figure 7).

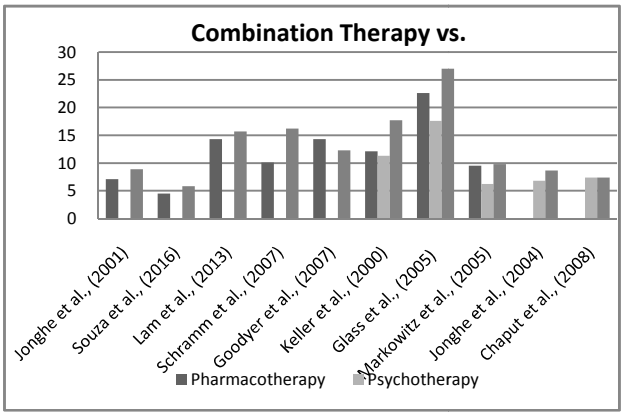

Figure 7 Changes in depression scalefor combination vs. either intervention

Dropout rates

The results for attrition rates don't seem to have a trend unlike other results. Six of the studies shown combination therapy as having a lower dropout rate than either monotherapy interventions with the biggest difference seen in Chaput *et al*., (2008) where 54.5% vs 9% were reported favouring the combination therapy.

Considering the different comparisons in each study, the mean is calculated through each group; 'studies that compared all three interventions', 'studies that only compared pharmacotherapy alone to combination therapy' and finally 'studies that compared psychotherapy alone to combination therapy'.

Firstly, for all three interventions that were directly compared; Keller *et al*., (2000),Glass *et al*., (2005) and Markowitz *et al*., (2005) showed that combination therapy had the least dropouts and psychotherapy had the most (18.1% vs 21.4% vs 25.7%).
Four studies directly compared pharmacotherapy alone with combination therapy in which the dropouts for the combination therapy had a mean of 12.98%; pharmacotherapy caused a dropout of 20.28% (Figure 8). Combination therapy proved its higher adherence rate again (13% vs 20.3%). Psychotherapy alone had three studies in which it was compared to combination therapy; attrition rates for combination therapy were a mean of 20.2%. Psychotherapeutic intervention caused a mean of 29.76%, again showing that combination therapy is superior in adherence (20.2% vs 29.8%).

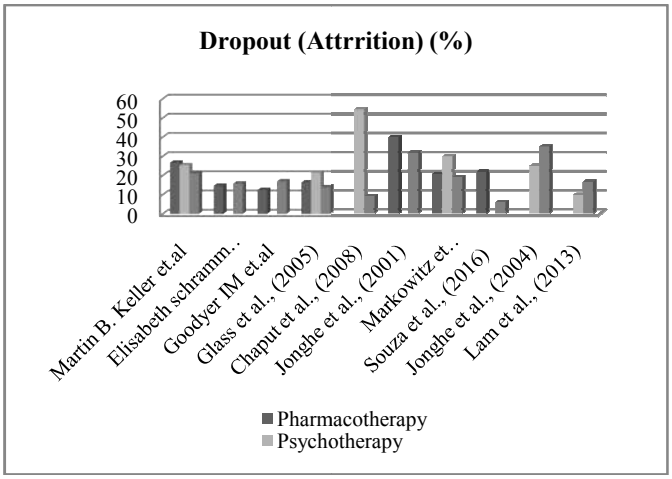

Figure 8 Dropout rates for combination vs either intervention

Limitations

The limitations for this study include the fact that some studies did not account for number of patients that responded or recovered due to treatment. The majority of studies did not compare three of the different active interventions between one another as it was more 'combination vs one alone intervention'. This is due to the lack of studies found that included this, or if found, generally being available to subscribers of the journal/website. The limited amount of data found on 'psychotherapy vs combination' was due to again lack of RCTs reproducible or carried out however the ones that were found showed that combination was considerably better. The DRS which had different forms didn't allow some studies to be directly compared with the majority which were HDRS/HAM-D.

CONCLUSION

The results from the data synthesis section in this dissertation allowed a direct comparison between two interventions which are standard treatment for depression. Ten studies were found in which the efficacy of either monotherapy was compared. From rates of response and remission we can see that both equally reduce depression severity in relatively equal amounts. The results from these studies showed that both interventions didn't have any significant difference in response (48.4% vs 47.1%) or remission (40.99% vs 42.36%). From these two measurements, it can be assumed that both interventions on their own are equal in efficacy.

When reduction in depression severity is included which is change from baseline to endpoint on a DRS, both interventions manage to averagely decrease a substantial amount of severity (difference of 1.4) favouring psychotherapy. Interestingly for Leff *et al*., (2000) there was a substantial difference in reduction (-16.4 vs -7.1) favouring psychotherapy, indicating at least for couples' therapy that its efficacy may be unmatched compared to antidepressants in patients who have depression and live with a critical partner. The difference in change of depression severity from baseline to endpoint varies from each study but this can be linked to time such as Dekker *et al*., (2008) in which the reduction was -4.21 (pharmacotherapy) however this study only lasted eight weeks whereas Elkin *et al*., (1989) lasted for double the amount of time and achieved a reduction of -12.2 (pharmacotherapy).

In one of the studies (Rohrichta *et al*., 2013) pharmacotherapy actually causes a slight increase in severity, however taken into

account the patients involved TRDand that the pharmacological intervention was TAU (antidepressant regime in which the patients continued their on-going treatment and wasn't monitored) whilst waiting for BPT after 12 weeks, this could lead to an increase in depressive symptoms with no change in treatment.

Taken into account safety and dropout rates, psychotherapy is more superior to pharmacotherapy with less dropouts (24.2% vs 33.53%). The increase in dropouts in pharmacotherapy can be linked to the increased side effects displayed due to antidepressants including nausea and vomiting. As more patients have dropped out, this reduces the chance of achieving the end goal of remission and makes the intervention less efficacious. In Leff *et al*., (2000) there was a massive difference in dropouts (15% vs 56.8%) with more than half of patients taking antidepressants dropping out. This may be due to the fact that the depression was linked with a critical partner and discussing issues through counselling allows for a better understanding of the disease and both partners were involved allowing increased support at home increasing adherence. The only study in which psychotherapy caused more dropouts was in Miranda *et al*., (2006) controlled study in which 64.5% dropped out in psychotherapy compared to 53%. Both dropout rates are high however psychotherapy may have had more due to all patients being low-income minority women who may have had difficulty understanding English and making it to the selected appointments; which may have created a barrier between patient and psychotherapist leading to a lack of efficacy and eventually adherence.

Throughout nearly all of the studies comparing psychotherapy and pharmacotherapy alone they were relatively equal in efficacy.

A further ten studies were found directly comparing combination with either intervention alone. More studies were found comparing the effects of combination with pharmacotherapy than with psychotherapy, so more data is available for the prior. Six of the studies included psychotherapy and seven included pharmacotherapy comparisons. Three studies directly compared all three interventions and from this the rates of response are showed: 41.36%, 55.63% and 67.03% with a trend that combination is superior to either intervention alone with psychotherapy being less efficacious. In only two studies (Markowitz *et al*., (2005) and Goodyer *et al*., (2007) did pharmacotherapy supersede combination and the response was near equal for both, the same cannot be said for psychotherapy which did significantly lower than both. The results here contrast from initial results comparing both monotherapies which showed that both interventions alone were equivalent in response.

Remission again showed a trend in which combination was superior to both interventions alone with only one out of the eight studies having a lower recovery rate (Goodyer *et al*., (2007)) than pharmacotherapy and this was near equal. Goodyer *et al*., (2007) was measured using CDRS-Rtscore as the population was adolescents which brands 'much improved' as response rate and 'very much improved' as remission which is vague and isn't as precise as HDRS.

Only two studies (Keller *et al*., (2000)and Markowitz *et al*., (2005)) directly compared all three interventions remission rates and from this data, its shown that combination therapy has a much higher rate of recovery than either intervention alone with only a third recovering from either intervention alone whereas over half entered remission for dual therapy.This is somewhat parallel to primary results comparing either monotherapy in which both alone interventions caused near equal mean remission rates albeit lower.

Concurring data from change in DRS showed that apart from Goodyer *et al*., (2007) and Chaput *et al*., (2008) all studies showed a larger decrease with combination therapy than any other intervention although some differences were small. Chaput *et al*., (2008) directly compared psychotherapy with combination and showed equal amounts of decrease in severity. The three studies that compared all three interventions together showed combination improves symptoms more than either intervention alone however in Markowitz *et al*., (2005) the difference in decrease is subtle (-0.3) making it insignificant and near equal. Glass (2005) had the biggest decrease with combination therapy however CDRS-rt was used which has different values from HDRS.

Disregarding these three studies and analysing the data for combination therapy vs pharmacotherapy showed a lower difference between the two but still favouring combination, similar results when comparing combination with psychotherapy alone where dual therapy has a slight advantage but small enough to question its clinical significance.

The number of patients that dropped out didn't seem to have a trend favouring combination unlike the other results collected however six of the possible ten studies had less dropouts occurring via combination therapy compared to either mono-intervention. Interestingly Chaput *et al*., (2008) had the largest difference with over half of patients who were treated with CBT dropping out compared to less than a tenth with combination therapy. This could be due to the fact that these patients suffered from treatment-refractory depression indicating for patients with resistant depression, dual therapy of medication and psychotherapy is more effective in these patients. This theory can be proven further by Souza *et al*., (2016) which had one of the biggest dropout differences between combination and pharmacotherapy indicating better adherence with dual therapy, this study also concerned patients with TRD. Increased adherence leads to an increased chance of recovery which is shown in Souza *et al*., (2016) remission rates, however Chaput *et al*., (2008) did not disclose data for this and both therapies managed to decrease equal amount of severity as seen on figure 7.

Considering the three studies that studied all three interventions, the attrition rate for the combination therapy is lower than individual therapies. From this direct comparison we can acknowledge that its more accepted and liked by patients than monotherapy. Pharmacotherapy did better than psychotherapy but worse than combination however with Chaput *et al*., (2008) high attrition rate for psychotherapy this may be a leading factor to a higher average.

In conclusion when compared alone they have similar benefits in reducing the symptom severity, although pharmacotherapy may reduce it faster initially. The number of patients withdrawing increased more with pharmacotherapy due to mainly adverse events from the drug. The contrasting effect of psychotherapy being less effective than pharmacotherapy when compared with combination and each other indicates further research may be needed.

Combination therapy proved more efficacious in producing a response and remission; however, changes in HDRS remain similar to a degree, asking the question is the difference in effectiveness clinically important? From this review it shows that further research is needed for this question, but combination is more effective, although not appropriate for every population. From attrition rates it is shown that combination therapy has increased adherence compared to either intervention alone.

Overall it can be said that combination is better than either intervention alone, but how much this affects the population, cost to the NHS and various other mitigating factors show that further research is needed.

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