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Abstract

Objectives: Brain injury may cause different physical and psychological problems, with depression being one of the commonest illnesses associated with brain injury. The aim of this research study is to analyse the effectiveness of non-pharmacological therapies in the treatment of depression in patients following brain injury. Study Design: This is a meta-analysis comparing pharmacological and non-pharmacological treatment of depression in patients with brain injury. Methods: Electronic data-base search, hand searching of journals and snowballing method was used to collect relevant data for the study. The only studies that have focused on treatment of depression in brain injury patients between the age of 16 - 64 years were included in this research. Results: Data analysis indicated that both modes of treatment are effective. There was no significant difference between pharmacological studies (pooled effect size d+ value is -0.37) and non-pharmacological studies (pooled effect size d+ value of -0.48). Test for heterogeneity is significant for both sets of data and no publication bias is detected for included studies. Conclusion: The results of the study suggest there is no difference in the efficacy of alternative therapies and pharmacological treatments for depression in patients with brain injury.

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Key words: Depression, brain injury, treatment, non-drug treatment and alternative therapies.

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Introduction

Mental health particularly depression has long been high on the government and public health agenda (Cassano and Fava, 2002). Treatment of depression within the community settings is favored by professionals avoiding unnecessary admissions to the hospital, with teams such as primary care and home treatment teams working in the community to treat those with depression (Gater, et al, 2010). Depression as a consequence of brain injury has specific characteristics and additional issues that may be particularly well treated within community settings.

Head injury is one of the most common causes of brain injury with 171,600 admissions to hospitals in England with a primary diagnosis of head injury between 2012 and 2103 (Health and Social Care Information Centre, 2013). The epidemiology of admission indicates 70% are males with an increasing number of patients admitted with head injuries aged ≥75 years (approaching 40%). Additionally 33-50% are children under 15 years of age (National Institute for Health and Care Excellence, 2014). Severe traumatic brain injury defined as Glasgow Coma Score (GCS) <9, has a bimodal presentation - 15-25 years and 65-75 years. This occurs in 11,000 people per year and has a mortality rate reaching 50% (Hammell and Henning, 2009). It is also known that admissions for head injury are from socioeconomically deprived areas (Tenant, 2005).

A person with acquired brain injury is more at risk of developing depressive illness during or after recovery (Babin, 2003). This occurrence could be due to stress and loss of ability to perform daily
routine life activities on the same scale prior to the brain injury. It is often noticed that people who have suffered from brain injury may also experience emotional distress and it is possible for those people to develop depressive illness (Fann, Uomoto and Katon, 2000; Fedoroff, et al., 1992; Hassan, et al., 2002). Other symptoms of depression often noticed in patients with brain injury include losing interest in daily activities, disturbed sleep pattern and eating disorder (Khan-bourne and Brown, 2003).

Antidepressants have been prescribed for a number of years by clinicians to treat depression and ‘tricyclic antidepressants’ (TCAs), ‘monoamine oxidase inhibitors’ (MAOIs) and ‘selective serotonin reuptake inhibitors’ (SSRIs) are commonly used antidepressants prescribed in clinical practice depending upon the severity and symptoms of the individual (Alderfer, Arciniegas and Silver, 2005; Berkow et al., 1997; Collier, Longmore and Scally, 2003). On the other hand, non drug therapies work in a different way with a decrease in symptoms of depression being achieved by building self-efficacy (Bandura, 1982) and personal motivation (Bandura and Schunk, 1981). Self efficacy is achieved through extensive learning, social experiences and determination of changing behaviour (Bandura, 1989). In addition, believing in one’s own capabilities to make positive changes plays a significant role that will assist in overcoming stress and depression through change in behaviour (Bandura, 1993; Zimmerman, Bandura and Martinez-Poss, 1992).

The non drug studies included in the meta analysis act to build self-efficacy in a number of ways. For example, Ouellet (2009) reports on the impact of volunteering, Powell (2002) investigates a community based outreach treatment from a multidisciplinary team involving clinicians, psychologists and social workers, and the impact of building coping mechanisms is discussed by Finest (2002). Other non drug treatments included in the meta-analysis are music therapy (Guetin, et al, 2009) and residential reintegration (Geurtsen, et al, 2008).

Antidepressants are not the best choice of treatment for depression in patients with brain injury due to the side effects of the drugs such as fatigue, loss of libido, sedation, poor concentration and toxicity of the drug (Brown, 2004). Furthermore, people with acquired brain injury are more prone to the side effects due to the structural and hormonal changes resulting from the injury. Therefore, alternative therapies should be considered for the treatment of depression in patients with brain injury (Brown, 2004). Choice of treatment for depression after brain injury should also be based upon the individual and their needs as to which form of therapy is best suitable (Fann et al, 2009). As the majority of people experiencing depressive illness who have acquired brain injury report a preference for non pharmacological treatment (Fann et al, 2009), it would therefore be beneficial to investigate the efficacy of alternative methods of treating depression in patients with brain injury.

This article aims to investigate and compare the efficacy of pharmacological and non pharmacological treatments for the treatment of depression following brain injury. As stated pharmacological treatments may not always be the best choice given that they work by adjusting hormone and neurotransmitter levels which may be disrupted as a consequence of the injury. Likewise non pharmacological treatments may be effective as they work on building confidence in competence which allows the patient to address the underlying behavioural causes of the depression.

Methods

This study was a meta analysis seeking to pool results from previously published work in order to compare efficacy of pharmaceutical and non pharmaceutical treatments of depression in patients with brain injury. A comprehensive electronic search of databases for the relevant literature was carried out. In addition, hand searching of material and snowballing method was also utilised to identify relevant literature.

Selection Criteria

The following selection criteria were applied to studies identified in the database search; studies from peer reviewed journals published within the last 10 years, persons who have suffered brain injury with a diagnosis of depression, age 16 - 64 years, and studies reporting pre and post study depression scores in treatment and control groups.

Data extraction

Standard deviation and mean of depression score were extracted from the selected studies as these
represent effect size. All but two included studies reported mean and standard deviation. Two studies (Ouellet, Morin and Lavoie, 2009; Powell, Heslin and Greenwood, 2002) reported mean and standard error. Thus standard deviation for these two studies was calculated from standard error using the formula described below: (Higgins and Green, 2009).

\[ SD = SE \times \sqrt{N} \]

Where two different treatment and control groups were reported within the same study, two different sets of data were extracted for analysis.

**Data synthesis**

Once the relevant data had been extracted from the studies selected for Meta analysis, this data was imported in the software named StatsDirect, version 2.7.8 for further analysis.

**Results**

Initially 1932 studies were found through database search. After eliminating duplicate studies (921), step by step inclusion criteria was applied to the rest of the studies and finally 24 studies were selected. Following further scrutiny of the studies 9 were excluded. In the remaining 15 studies the total number of participants receiving either drug or non drug treatment was 538, with 564 participants in the control group.

**Effect size: meta-analysis of drug data**

Six studies with a total of 150 patients had antidepressant drug treatment. All studies included in the analysis indicate that antidepressants are effective for treating depression following brain injury. Meta analysis results reveal pooled effect (d+ = -0.37, CI= -0.610725 to -0.137906) and overall effect (Z=3.103281, p = 0.0019) suggesting that the use of antidepressants in the treatment of depression following brain injury is effective. Heterogeneity (I² = 86.5%, Q = 36.98, p <0.0001) is at significant level and no publication bias (Kendall’s tau = -0.6, p = 0.0556) is detected.

The forest plot in Figure 1 shows these results. The vertical dotted line in the graph (to the left of the line of 0) represents the center of 95% CI range of pooled effect size.

**Figure 1: Effect size Meta analysis forest plot for drug data**

As can be seen in Figure 1, most of the studies are plotted nearby vertical dotted line (to the left of 0). Whilst the 95% CI for included studies may span the solid vertical line of 0 (no effect) the pooled effect size CI (D+ -.0610725 to -0.137906) does not cross the line of no effect allowing us to conclude the overall efficacy of drug treatment.

**Effect size: meta analysis of non drug data**

In 12 studies, a total 388 patients with depression and brain injury have received different types of non drug treatment therapies to manage depression. All but one of the studies (Powell, Heslin and Greenwood, 2002) indicates that non drug treatments are effective in the treatment of depression following brain injury.
Effect size meta-analysis plot [fixed effects]

Tiersky, et al. 2005
Powell, et al. 2002
Medd and Tate, 2000
Guertsen, et al. 2008
Finset and Andersson, 2000
Bradbury, et al. 2008
Bradbury, et al. 2008
Arundine, 2009

pooled effect size = -0.483956  (95% CI = -0.626614 to -0.341297)

Figure 2: Effect size meta analysis forest plot for non drug data

Combining the results of the 12 included studies yields a pooled effect (d+ = -0.48, CI = -0.626614 to -0.341297) and overall effect (Z -6.64900 8, p = 0.0001) indicating the efficacy of non drug therapies in the treatment of depression following brain injury. As with the analysis of studies investigating drug treatment, whilst the 95% CI for included studies may span the solid vertical line of no effect, the pooled effect size CI (-0.626614 to -0.341297) does not cross the line of no effect allowing us to conclude the overall efficacy of non drug treatment.

Statistical test for heterogeneity is significant (I^2 = 47.6%, Q = 20.99, P = 0.0334) and no publication bias is detected (Kendall’s tau = -0.09, p = 0.6384).

Comparison of drug and non drug data analysis

In order to answer the main question to compare efficacy of drug and non drug treatments in the treatment of depression following brain injury, the outcomes of the two meta analyses were compared. This was achieved by examining the difference of mean between the two treatment groups to advocate the effectiveness of treatment with one or the other method (Higgins and Green, 2009). In this case standardised mean difference (SMD) which is Hedges-Olkin statistic (StatsDirect, 2009) is taken into account for the comparison of two treatment groups. SMD can be calculated for each study by dividing the difference of two means with standard deviation, and allows comparison of means when the mode of measurement differs as in the measurement of depression.

Table 1 compares SMD of non drug and drug data. Stratum refers to the study number in the two sets of meta analysis; the table also contains a column for SMD with 95% CI for each of the included studies.

Table 1: Comparison of drug and non drug SMD

<table>
<thead>
<tr>
<th>Stratum</th>
<th>g (SMD) non drug data</th>
<th>95% CI</th>
<th>g (SMD) drug data</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.32839</td>
<td>0.650662</td>
<td>-0.258961</td>
<td>0.873474</td>
</tr>
<tr>
<td>2</td>
<td>0.670442</td>
<td>1.028459</td>
<td>0.310327</td>
<td>3.654407</td>
</tr>
<tr>
<td>3</td>
<td>1.074094</td>
<td>2.388784</td>
<td>0.296580</td>
<td>-0.025866</td>
</tr>
<tr>
<td>4</td>
<td>-1.44588</td>
<td>2.833926</td>
<td>0.008401</td>
<td>1.333401</td>
</tr>
<tr>
<td>5</td>
<td>0.396379</td>
<td>0.729338</td>
<td>0.062137</td>
<td>0.068111</td>
</tr>
<tr>
<td>6</td>
<td>-0.601875</td>
<td>1.177267</td>
<td>0.019524</td>
<td>0.376323</td>
</tr>
<tr>
<td>7</td>
<td>0.379758</td>
<td>1.151427</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>0.461092</td>
<td>1.447828</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>-0.684461</td>
<td>1.008759</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>0.529886</td>
<td>0.948025</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>0.289432</td>
<td>0.117799</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>-1.199938</td>
<td>2.149089</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

In order to determine the most effective treatment, a comparison of SMD seen in Table 1 is made. Higher scores represent more severe depression whilst lower scores suggest mild depression.

It can be seen from Table 2 that in the majority of cases, studies reporting non drug treatments report lower SMD. However, this on its own is not sufficient to assess the difference between the two treatment groups.
Table 2: Comparison of drug and non drug data
Meta analysis results

<table>
<thead>
<tr>
<th>Results</th>
<th>Drug data</th>
<th>Non drug data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pooled effect size d+</td>
<td>Pooled effect size d+</td>
</tr>
<tr>
<td></td>
<td>-0.374316 (95% CI = -0.610725 to -0.137906)</td>
<td>-0.483956 (95% CI = -0.626614 to -0.341297)</td>
</tr>
<tr>
<td></td>
<td>Z(test d+ differs from 0)</td>
<td>Z(test d+ differs from 0)</td>
</tr>
<tr>
<td></td>
<td>-3.103281 P = 0.0019</td>
<td>-6.640008 P &lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>Cochran Q</td>
<td>Cochran Q</td>
</tr>
<tr>
<td></td>
<td>36.981816 P &lt; 0.0001</td>
<td>20.993852 P = 0.0334</td>
</tr>
<tr>
<td></td>
<td>I² (inconsistency)</td>
<td>I² (inconsistency)</td>
</tr>
<tr>
<td></td>
<td>86.5% (95% CI = 70.4% to 92%)</td>
<td>47.6% (95% CI = 0% to 71.6%)</td>
</tr>
<tr>
<td></td>
<td>Begg-Mazumdar: Kendall’s tau</td>
<td>Begg-Mazumdar: Kendall’s tau</td>
</tr>
<tr>
<td></td>
<td>-0.6 P = 0.0556</td>
<td>-0.090909 P = 0.6384</td>
</tr>
<tr>
<td></td>
<td>Egger: bias</td>
<td>Egger: bias</td>
</tr>
<tr>
<td></td>
<td>-4.786308 (95% CI = -7.05897 to -3.47058)</td>
<td>-0.59926 (95% CI = -2.64772 to 1.4492)</td>
</tr>
<tr>
<td></td>
<td>P = 0.0888</td>
<td>P = 0.5292</td>
</tr>
</tbody>
</table>

Comparison of the pooled effect (D+) would suggest the superior efficacy of one treatment over the other, although as both sets of analysis yield significant overall effect (Z) it is not possible within the confines of this analysis to draw firm conclusions regarding which treatment regime is most effective.

Discussion

The meta analysis of drug and non drug data was carried out to investigate if alternative therapies are more effective than antidepressants for the treatment of depression in patients following brain injury. The results indicate that both treatment methods are effective with high significant values, however, as CIs of the two treatment methods overlap greatly, it cannot be said that one treatment option is better than the other.

The research studies included in the meta analysis of non drug data have applied different treatment options such as; music therapy, cognitive behavioural therapy (CBT), psychotherapy and rehabilitation processes with coping mechanisms that have been shown to be effective in individual studies. The studies (Ashman et al., 2009; Fann, Uomoto and Katon, 2000; Lee et al., 2005) that are included in the meta analysis of drug data have mainly used antidepressants from the SSRI group. The choice of antidepressant drug is limited for managing depression in patients with brain injury due to the side effects of the pharmacological drug (Alderfer, Arciniegas and Silver, 2005; Berkow et al., 1997; Collier, Longmore and Scally, 2003). It is already established that people with brain injury are more prone to side effects due to imbalanced chemical reaction caused by the brain injury (Brown, 2004). Pooled results of different non drug treatment methods used to manage depression indicate that alternative therapies are effective for the treatment of depression. The meta analysis results indicate that both antidepressants and non drug therapies are highly effective when used to treat depression in patients with brain injury, whilst the meta analysis result of both sets of data does not provide enough evidence to conclude that one treatment option is more effective than the other.

However, individuals suffering from depressive disorder after brain injury report a preference for psychotherapy, behavioural therapy, physical exercise and counseling due to lack of side effects experienced with drug treatments (Fann et al., 2009). Evidence of the effectiveness of alternative therapies is reported here. This may be because depression in patients with brain injury is a secondary depression (Babin, 2003). Often people with brain injury have difficulty in performing daily routine activities and getting back into social life, which puts psychological pressure on individuals and they start falling into depression. Alternative therapies work effectively because people with brain injury learn how to cope and manage in social and daily life through CBT programs and psychotherapies, thus the efficacy of alternative therapies cannot be overlooked. This study of effectiveness of non drug therapies contributes to the growing debate of efficacy of alternative therapies that are applied to manage depression in patients with brain injury. The alternative therapies help bring about an improvement in an individual to function well in social, work and daily routine life.

The research findings suggest that alternative therapies are as effective as drug treatment methods; alternative therapies can be used effectively to complement pharmacological treatment of depression in patients with brain injury.
Furthermore, an individual can benefit from alternative therapy straight away whereas pharmacological treatment takes a minimum of two weeks before the effect can be appreciated. It has been established that people with brain injury are at higher risk of falling into depression due to the difficulty of functioning well in their routine life so alternative therapies with their various mechanisms of action can work alongside antidepressants to produce efficient results. Community based interventions such as those included in this meta analysis include volunteering (Ouellet, Morin and Lavoie, 2009), community based outreach treatment from a multidisciplinary team involving clinicians, psychologists and social workers (Powell, Heslin and Greenwood, 2002), coping (Finest and Andersson, 2000), music therapy (Guetin et al, 2009), and residential reintegration (Geurtsen et al, 2008), and are delivered by a range of professionals with a variety of backgrounds and training. As these are seen to be as effective as drug treatments they may be more acceptable to service users because barriers to accessing treatment such as location, fear of stigmatisation from having a psychiatric record and adverse side effects of drugs, are eliminated or minimised.

A smaller number of studies on drug treatment method (6) than non drug treatment method (12) with different sample sizes within the studies is one of the limitations that might have affected the meta analysis results. Moreover, CI range and pooled effect size estimate values may vary with the number of studies included for meta analysis and different sample size of participants. The relatively small number of participants (total of 538) in the treatment group is another limitation noticed in this study because a small sample of participants may not provide perfect data analysis results. Moreover high levels of heterogeneity probably as a result of differing methodologies, treatments and outcome measures may have affected the results. Some of the researchers have used single and double blinding in their study whereas others have not used any blinding which is both a strength and a limitation and could be a source of bias for individual studies which could in turn impact the validity and reliability of the meta analysis.

Conclusion

Meta analysis results of drug and non drug data suggest that both treatment methods are effective when used to treat depression and aggregate results of meta analysis is supported with the findings of individual studies that report the effectiveness of treatment method used. The results of both sets of data are compared to investigate the research question of whether or not alternative therapies are an effective and superior mode of treating depression in patients with brain injury. After comparing the meta analysis results of drug and non drug data it is concluded that, although pooled effect size d+ value of drug and non drug data differ but 95% CI range of both sets of data overlap, caution should be exercised in determining which treatment is superior.

Interventions utilising both pharmaceutical and non pharmaceutical treatments based on patient need and accommodating preference should be developed. The use of community based treatments delivered and supported by independent and appropriately qualified individuals and community organisations is suggested. Within the current climate of providing care in the community, non drug treatments as included in this study and described above are to be encouraged. We suggest this not only because they are effective, acceptable and accessible, but they would by their nature involve self-employed or community employed practitioners as opposed to statutory service providers such as NHS and local government.

References


