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Physical Co-morbidity among Treatment Resistant vs. Treatment Responsive Patients with Major Depressive Disorder

Amittal D\(^1\), Fostick L\(^2\), Silberman A\(^3\), Calati R\(^4\), Spindelegger C\(^5\), Serretti A\(^4\), Juven-Wetzler A\(^3\), Souery D\(^6\), Mendlewicz J\(^7\), Montgomery S\(^8\), Kasper S\(^5\), Zohar J\(^3\)

1 - Department of Psychiatry 'B', Ness-Ziona Mental Health Center, Tel-Aviv University, Ness-Ziona, Israel
2 – Ariel University Center, Ariel, Israel
3 - Sheba Medical Center, Tel Hashomer, Israel
4 – Institute of Psychiatry, University of Bologna, Bologna, Italy
5 – Department of Psychiatry and Psychotherapy, Medical University Vienna, Austria
6 – Laboratoire de Psychologie Medicale, Universite´ Libre de Bruxelles and Psy Pluriel, Centre Europe´en de Psychologie Medicale, Brussels, Belgium
7 – Universite´ Libre de Bruxelles, Belgium
8 – Imperial College School of Medicine, London, UK
Abstract

Co-morbid physical illness has been suggested to play an important role among the factors contributing to treatment resistance in patients with major depressive disorder. In the current study we compared the rate of physical co-morbidity, defined by ICD-10, among a large multicenter sample of 702 patients with major depressive disorder. A total of 356 of the participants were defined as treatment resistant depression (TRD) patients – having failed two or more adequate antidepressant trials. No significant difference was found between TRD and non-TRD participants in the prevalence of any ICD-10 category. This finding suggests that although physical conditions such as diabetes, thyroid dysfunction, hypertension, ischemic heart disease, and peptic diseases are often accompanied by co-morbid MDD, they do not necessarily have an impact on the course of MDD or the likelihood to respond to treatment. Marginally higher rates of co-morbid breast cancer, migraine and glaucoma were found among TRD participants. Possible explanations for these findings and their possible relation to TRD are discussed.

Keywords: Depression; Treatment Resistance; Treatment Response; Medical Comorbidity
Major depressive disorder (MDD) is a common disorder affecting 5-9% of women and 1-2% of men, characterized by symptoms of loss of interest and pleasure from daily activities, changes in body weight, sleep disturbances, loss of energy, concentration problems, and suicidal thoughts (DSM-IV, 1994). Major depressive disorder has a negative impact on one’s quality of life, and carries, particularly among males, a high risk of suicide. Even when adequately treated, up to half of all patients do not respond to first-line monotherapy and 60-70% of depressed patients fail to reach complete remission (Sackheim, 2001). Despite rapid development in the therapeutic armamentarium of mood disorders since the late 1980’s (Fredman et al., 2000; Kocsis, 2000), treatment resistant depression (TRD) incorporates well over a third of depressed patients (Fava and Davidson, 1996) and have larger financial impact (Crown et al., 2002; Greenberg et al., 2003, 2004; Fostick et al., 2010; Russell et al., 2004).

Studies suggested several risk factors to the non-responsiveness and the poor outcome of TRD. These include decrease of social support (Bosworth et al., 2002), poor social adjustment, poor social relationships (Freedman et al., 1995), and negative life events (Kohn et al., 2001; Amital et al., 2008). Psychiatric co-morbidity was also related to TRD, with a broad range of symptoms and disorders, including psychotic features (Glassman et al., 1975; Schatzberg and Rothschild, 1992), substance abuse, bipolar disorder (Berlim & Turecki, 2007; Crown et al., 2002), anxiety (Berlim & Turecki, 2007; Crown et al., 2002; Davidson, 2002; Souery et al., 2007), life-time panic disorder and agoraphobic spectrum symptoms (Brown, 1996; Souery et al., 2007), and
personality disorder was found to be related to TRD in some studies (Souery et al., 2007; Shea et al., 1999; Stek et al., 2002), but not in others (Petersen et al., 2002). Also, concomitant use of anxiolytics (Bosworth et al., 2002; Frank et al., 2000), more hospitalizations, outpatient visits, and use of psychotropic medications were found to be related to TRD (Crown et al., 2002; Amital et al., 2008).

Physical illness was often considered a potential contributing factor to the occurrence of TRD (Berlim & Turecki, 2007; Keitner et al., 1991). Co-morbid MDD and hypercholesterolemia were found to be associated with poor response to antidepressant (Sonawalla et al., 2002; Papakostas et al., 2003). Arthritis and circulatory problems were also found to be related to a worse outcome of depression (Oslin et al., 2002). Moreover, longitudinal studies have suggested that MDD patients with comorbid physical illness may be at a greater risk for a chronic course of depression or of incomplete recovery, as compared to MDD patients with no other physical illness (Keitner et al., 1991; Akiskal et al., 1981).

Other studies have suggested that patients with co-morbid physical illness have a rate of symptom response to antidepressant that is comparable to that of patients without co-morbidity (Small et al., 1996). For example, Miller et al. (2002) failed to show any relationship between cardiovascular risk factors and poorer MDD outcome. Papakostas et al. (2003) designed a study to test whether the presence of physical co-morbidity can predict treatment response in TRD patients. They found no difference in response between TRD patients with or without physical co-morbidity. Similar findings were found by others (Perlis et al., 2004; Evans et al., 1997; Small et al., 1996).
A different perspective to the linkage between physical condition and response to anti-depressant could be reached by studying physically ill patients with co-morbid depression. The depressive symptoms of patients with severe medical illness were less likely to respond to (open) treatment with Fluoxetine than those patients with minor or no physical condition (Popkin et al., 1985). In diabetic patients, presence of depression was associated with poor glucose control and influenced patients' compliance to anti-diabetic treatment (Kornstein et al., 2000). However, when the associated depression is adequately treated with psychotropic drugs, there is usually an improvement in the somatic symptoms as well (Gruber et al., 1996).

A large majority of studies investigating the relationship between TRD and co-morbidity have focused on differences between TRD patients with and without co-morbidity, and whether physical co-morbidity affects response to treatment. The results of these studies are not conclusive. In the current study we aim to answer the question of the relationship between physical co-morbidity and TRD by adapting a different perspective, namely comparing physical co-morbidity among TRD and non-TRD patients. In order to answer this question adequately, we used international data from the European multicenter study on TRD (see also Souery et al., 2007) that was conducted on 702 patients meeting DSM-IV criteria for MDD. The patients were divided to TRD and non-TRD subjects, according to a well-established criterion (Souery et al., 1999), and their physical co-morbidity was explored.

There are many definitions of TRD – the more recent ones include those of Thase and Rush (1997), Souery et al., (1999), the European Union's committee for Propriety
Medicinal Products (CPMP, 2002), and Fava (2003). Thase and Rush (1997) proposed a model of staging the different levels of resistance based on the number of failed therapeutic attempts. Fava et al. (2003) proposed an alternative staging model (Massachusetts General Hospital Staging Model (MGH-S)) which scores resistance on a continuous scale ranging from 0 to 5. In this scale, 1 point is given per treatment, 0.5 points is given for each augmentation strategy applied, and 3 points are given for ECT. In 2002, the European Union's committee for Propriety Medicinal Products (CPMP) defined TRD as a failure to respond to the second treatment out of two consecutive products of different classes given at an adequate dose and for a sufficient length of time. This definition was also used by Souery et al. (1999) in their large European multicenter study, and was adapted in the current study as it enables differentiating MDD patients into two groups, according to their response to treatment.
Experimental Procedures

The data for this study is derived from an international multi-center epidemiological survey, designed by the Group for the Study of Resistant Depression (GSRD) to examine the characteristics of TRD patients versus non-TRD patients. The survey was carried out in Belgium, France, Italy, Austria, and Israel during the years 2000-2004 (see also Souery et al., 2007).

Participants Out of 955 patients screened for the study, 702 met DSM-IV criteria for current MDD and were included in the study after signing informed consent. All of the 702 patients were over 18 years old, were inpatients or outpatients, and received at least one 4-week adequate antidepressant treatment at optimal dose. According to the definition used in the study, TRD required a failure of at least two consecutive adequate antidepressant treatments. Non-response to treatment was defined as a total Hamilton Depression Rating Scale score higher than 16. Consequently, 346 patients were defined as non-TRD, and 356 patients were defined as TRD. TRD participants had lower rate of SSRI usage in their last episode, as compared with non-TRD participants (43% vs. 60%, $\chi^2(1)=19.7$, $p<.001$), but among both groups, 20% of the patients had psychotherapy in their last episode ($\chi^2(1)=.042$, n.s.). Both groups also had similar mean delay time between the onset of the last episode and start of treatment (79.8 day for TRD and 69.7 days for non-TRD participants, $t_{(510)}=.49$, n.s.).

Questionnaires Patients' current and lifetime psychiatric diagnoses were obtained using the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Severity of depression was assessed using Hamilton Depression Rating Scale
(HDRS) (Hamilton, 1960). In addition, patients’ demographics, history of hospitalizations and treatments, and current medical co-morbidity was collected in an interview.

**Procedure** Each patient underwent an interview with a psychiatrist. The interview included the above mentioned questionnaires and lasted about 45 minutes. The study was approved by the local IRB committee of each center, and signed informed consent was given in the beginning of the session. Physical co-morbidity was specified for each patient during the interview. This data was later transformed into the WHO's International Classification of Diseases version 10 (ICD-10) classification by two independent investigators (DA and AS).

**Statistical analysis:** Data analysis was done using SPSS 17 software (SPSS Inc.; Chicago, Ill.). Study groups (TRD and non-TRD) were compared on demographic variables, variables of disease severity, and existence of physical and co-morbidity. In order to assess statistical significance of categorical variables, a Chi-square test was obtained. A t-test for independent samples was used for continuous variables. To control for possible confounders, a logistic regression was performed including in the model in turn all possible stratification factors possibly influencing TRD status.
Results

The prevalence of co-morbidity, according to ICD-10 classification, was compared between TRD and non-TRD participants, to test whether there are differences in physical co-morbidity between the groups. No significant difference was found between TRD and non-TRD participants in the prevalence of any ICD-10 category (see table 1), although the difference between TRD and non-TRD patients in the prevalence of Infectious and Parasitic Diseases and Diseases of the Nervous System and Sense Organs, was marginally significant.

Physical co-morbidity was found in 147 (41%) TRD participants and 140 (40%) non-TRD participants ($\chi^2(1) = .171, \text{n.s.}$). The distribution of the number of co-morbidities was also similar between TRD and non-TRD participants ($\chi^2(1) = 1.844, \text{n.s., table 2}$). To control for possible stratification factors, we included variables possibly associated with TRD, such as age, age at onset, Axis I and II comorbidities, suicidal behavior, and severity into the logistic regression model. None of these variables significantly influenced the results.

A closer look was taken at the specific diseases reported by the participants (rather than the categories included), and categories with prevalence of more than 20 participants of the study group, namely Neoplasms, Endocrine, Nutritional and Metabolic Diseases, and Immunity Disorders, Diseases of the Nervous System and Sense Organs, Diseases of the Circulatory System, Diseases of the Digestive System were included into an additional statistical analysis. The diseases with a prevalence of at least five in the study group are stated in table 3. No significant differences were
found between TRD and non-TRD groups, although higher prevalence of breast cancer among TRD group was marginally significant. No statistical analysis was conducted on Glaucoma and Migraine due to a small number of participants.
Discussion

The major finding of the study is that no difference between TRD and non-TRD in physical co-morbidity was found, when asking in a subjectively self-reported design. Although MDD is sometimes a poor prognostic sign to a physical illness (Connerney et al., 2010; Rost et al., 1998) and in previous studies TRD was related to higher medical costs, even when controlled for symptoms severity (Fostick et al., 2010), in this study the complementary finding – increased physical comorbidity in TRD patients – was not found. Moreover, some symptoms in MDD, such as weight loss, weight gain, changes in appetite, insomnia, hypersomnia, or fatigue show physical manifestation (DSM-IV, APA, 1994).

TRD is effectively an untreated MDD. Therefore, an intuitive expectation is that TRD will be associated with more physical illness. This hypothesis was not confirmed by the findings of this study and findings of previous study that found higher response rate among MDD patients with axis-III co-morbidity, as compared to general MDD population (Iovieno, Tedeschinia, Amerala, Rigatellic, Papakostas, 2011). Findings from the STAR*D study show that more physical conditions are related to poorer remission among MDD patients (Rush et al., 2008; Trivedi et al., 2006). The apparent discrepancy might be related to differences in study design (prospective vs. retrospective in the current study), tool to measure physical co-morbidity (vs. self-report specification of diseases in the current study), and the study population (poor remission vs. TRD in the current study). Each of these differences could be enough to lead to different results, all the more so all of them.
The current study was carried out in a self-report design. Therefore, the data collected in this study does not reflect objectively all the physical symptoms the participants endure. However, it represents the symptoms that were significant enough to the participant to be reported which give rise to an interesting picture. Furthermore, another limitation is that some of the diseases and ICD-10 categories occurred only in a small number of participants. The infrequent occurrences can be explained by a low prevalence of these diseases, which require much larger sample size than the 702 included in the current study.

A closer look at the specific diseases reported revealed some interesting findings. Although diabetes, thyroid dysfunction, hypertension, ischemic heart disease, and peptic diseases are often accompanied by co-morbid MDD (e.g., Fisher et al., 2008; Fornaro et al., 2010; Shen et al., 2010), they were not found to be associated with TRD in the current study. This finding suggests that although these physical conditions may lead to MDD, they do not necessarily have an impact on the course of the disease and the likelihood to respond to a treatment. However, as reported earlier, depression might worsen the course of physical illness if not treated (for example, cardiovascular). Indeed, the American Heart Association suggests that every patient having suffered heart failure should be treated for MDD (Litchman et al., 2008).

The data of the current study point to three diseases that might be related to TRD – Breast cancer, migraine and glaucoma. For none of these conditions there is a clear straight-forward explanation, and possible relation to TRD does not necessarily imply that these diseases overlap each other. Speculations could range from physical illness as a trigger factor for psychiatric diseases (e.g. depression as a secondary response to
breast cancer) to a common pathway of the physical and psychiatric disorder (e.g. resilience). In this study, breast cancer was found to be more prevalent among TRD participants, with marginal significance (apparently due to a small number of observations). This finding might reflect a secondary effect of breast cancer, or provide a hint regarding a common pathway of this physical disorder and depression (resilience).

Moreover, a numeric finding of higher prevalence of migraine and glaucoma among TRD in this study deserves a short discussion. Studies have shown that migraine is often associated with MDD, and patients with migraine are at a higher risk of suicide than the general population (Breslau et al., 1991). In addition, the prevalence of MDD in migraine patients was found to be much higher than in control patients (Devlen, 1994, Evans et al., 2008). Breslau et al. (1991, 2003) have demonstrated a two-way association between MDD and migraine over a two year period; the incidence of migraines was raised when MDD was present, and *vice versa*. However, the relationship between glaucoma and TRD remains unclear. Further investigations concerning the pathology in glaucoma and its relation to TRD are therefore needed.

In conclusion, this study shows an increased morbidity in TRD (based on self-reports) in selected diseases (Breast cancers, migraine and glaucoma). However, a simple correlation between TRD and physical comorbidity was not found, even when considering possible stratification factors. The findings of the current study suggest that further research should be focused on physical morbidity among TRD patients, especially with regard to breast cancer, migraine and glaucoma. Moreover, the
difference between the finding from a self-report design and previous studies, which used medical records, should be investigated in further studies.
REFERENCES


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Sheehan DV: The Anxiety Disease. New York, Scribner’s, 1983


Table 1. Prevalence of physical co-morbidity among TRD and non-TRD participants, by ICD-10 categories

<table>
<thead>
<tr>
<th>ICD-10 Category</th>
<th>TRD</th>
<th>Non-TRD</th>
<th>$\chi^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious and Parasitic Diseases (001-139)</td>
<td>6</td>
<td>1</td>
<td>3.571</td>
<td>.059</td>
</tr>
<tr>
<td>Neoplasms (140-239)</td>
<td>12</td>
<td>12</td>
<td>.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Endocrine, Nutritional and Metabolic Diseases, and Immunity Disorders (240-279)</td>
<td>48</td>
<td>42</td>
<td>4.000</td>
<td>.527</td>
</tr>
<tr>
<td>Diseases of the Blood and Blood-Forming Organs (280-289)</td>
<td>2</td>
<td>3</td>
<td>2.000</td>
<td>.655</td>
</tr>
<tr>
<td>Diseases of the Nervous System and Sense Organs (320-389)</td>
<td>17</td>
<td>8</td>
<td>3.240</td>
<td>.072</td>
</tr>
<tr>
<td>Diseases of the Circulatory System (390-459)</td>
<td>19</td>
<td>23</td>
<td>.381</td>
<td>.537</td>
</tr>
<tr>
<td>Diseases of the Respiratory System (460-519)</td>
<td>8</td>
<td>9</td>
<td>.059</td>
<td>.808</td>
</tr>
<tr>
<td>Diseases of the Digestive System (520-579)</td>
<td>23</td>
<td>23</td>
<td>.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Diseases of the Genitourinary System (580-629)</td>
<td>2</td>
<td>2</td>
<td>.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Complications of Pregnancy, Childbirth, and the Puerperium (630-679)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diseases of the Skin and Subcutaneous Tissue (680-709)</td>
<td>2</td>
<td>1</td>
<td>.333</td>
<td>.564</td>
</tr>
<tr>
<td>Diseases of the Musculoskeletal System and Connective Tissue (710-739)</td>
<td>7</td>
<td>11</td>
<td>.889</td>
<td>.346</td>
</tr>
<tr>
<td>Congenital Anomalies (740-759)</td>
<td>8</td>
<td>5</td>
<td>.692</td>
<td>.405</td>
</tr>
<tr>
<td>Category</td>
<td>Value_1</td>
<td>Value_2</td>
<td>Value_3</td>
<td>Value_4</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Certain Conditions Originating in the Perinatal Period (760-779)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms, Signs, and Ill-Defined Conditions (780-799)</td>
<td>5</td>
<td>5</td>
<td>.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Injury and Poisoning (800-999)</td>
<td>3</td>
<td>2</td>
<td>.200</td>
<td>.655</td>
</tr>
</tbody>
</table>
Table 2. Distribution of number of comorbidities among TRD and non-TRD participants

<table>
<thead>
<tr>
<th>No. of physical comorbidities</th>
<th>TRD</th>
<th>Non-TRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>209 (58.7%)</td>
<td>205 (59.2%)</td>
</tr>
<tr>
<td>1</td>
<td>95 (26.7%)</td>
<td>99 (28.6%)</td>
</tr>
<tr>
<td>2</td>
<td>37 (10.4%)</td>
<td>33 (9.5%)</td>
</tr>
<tr>
<td>3</td>
<td>14 (3.9%)</td>
<td>8 (2.3%)</td>
</tr>
<tr>
<td>4</td>
<td>1 (.3%)</td>
<td>1 (.3%)</td>
</tr>
</tbody>
</table>
Table 3. Diseases whose prevalence was at least five among TRD and non-TRD participants

<table>
<thead>
<tr>
<th>Disease</th>
<th>TRD N=356</th>
<th>Non-TRD N=346</th>
<th>$\chi^2$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>9 (69%)</td>
<td>4 (31%)</td>
<td>3.222</td>
<td>.073</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14 (56%)</td>
<td>11 (44%)</td>
<td>.158</td>
<td>.691</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>30 (51%)</td>
<td>29 (49%)</td>
<td>.181</td>
<td>.671</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>5 (83%)</td>
<td>1 (17%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine</td>
<td>5 (100%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>48 (52%)</td>
<td>44 (48%)</td>
<td>.002</td>
<td>.962</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>11 (48%)</td>
<td>12 (52%)</td>
<td>.225</td>
<td>.635</td>
</tr>
<tr>
<td>Peptic disease</td>
<td>14 (64%)</td>
<td>8 (36%)</td>
<td>.560</td>
<td>.454</td>
</tr>
</tbody>
</table>