TREATMENT-RESISTANT DEPRESSION AND THE ELEPHANT IN THE ROOM

by

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ABSTRACT

Depression is a complex disorder associated with significant health, social, and economic burdens. Current treatments are not effective in producing remission in a large proportion of those diagnosed with this illness, resulting in a high prevalence of treatment-resistant depression (TRD), a form of depression associated with significant disease burden. A scoping review of the literature was conducted to identify the treatment paradigms currently being utilized to address TRD. The findings indicate that despite evidence of the biological, psychological, and social factors surrounding depression, our treatment approaches are detrimentally narrow, with little research addressing the psychological or social realms of the disorder. Additionally, systematic barriers to certain treatment approaches exist, limiting access to care and hindering optimal treatment outcomes. Efforts to expand the scope of research and advocate for structural changes that support well-being are necessary to reduce the substantial burdens associated with TRD and promote the health of our population.

Keywords: depression; treatment-resistant depression; population health; scoping review; treatment paradigms

DEDICATION

This paper is dedicated the two people in my life whose support has made this work possible. To my Mom- thank you for inspiring this project and for consistently demonstrating perseverance and strength. To Garry- thank you for always believing in and encouraging me and for always taking the time to make me smile.

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1: INTRODUCTION

"Depression is the product of a complex interaction between biological, psychological and social elements" - Patten and Juby, 2008

Depression is a prevalent and disabling disorder that is often under-diagnosed and poorly treated (World Health Organization [WHO], 2003; WHO, 2008). It is commonly comorbid with other physical and mental illnesses further impacting treatment outcomes and quality of life (Kessler et al., 2003). Despite the availability of a number of evidence-based treatments for depression, up to 70% of the population diagnosed with depression will not experience symptom remission, and come to be classified as experiencing treatment-resistant depression (TRD) (Greden, 2001). Yet, despite the significance of TRD, relatively little is known about the treatment approaches that would be most effective in addressing it. This paper presents the results of a scoping review of the scientific literature. The purpose of this study is to identify the current state of research on the treatment approaches to TRD. Further, it is hoped that the findings from this study can be used in knowledge exchange ventures to influence policy and practices and fuel needed change. In light of the limited research surrounding the risk factors and burdens associated with TRD, relevant literature will be drawn from the broad and extensive depression literature and presented as a background for the discussion of TRD.

2: BACKGROUND

2.1 Burden of Disease

In recent years, mental illnesses have emerged from the shadows and come to be identified as one of the greatest contributors to the global burden of disease (WHO, 2008). One of the factors contributing to this recognition is the World Health Organization's (WHO) Global Burden of Disease studies which identify the leading causes of morbidity and mortality worldwide[1]. In 2003, the WHO released a report stating that neuropsychiatric conditions (which include dementia, mental retardation, depression, schizophrenia, and epilepsy, amongst others) constitute approximately 19% of the global burden of disease (WHO, 2003), a considerable increase over the 1999 estimate of 13% (WHO, 1999).

Of the neuropsychiatric conditions identified in the WHO report, major depression (henceforth referred to as depression) is identified as being the most prevalent. According to a nationally representative survey conducted in the United States (US), the lifetime prevalence of depression is 16.2% and the 12-month prevalence 6.6% (Kessler et al., 2003). In Canada, the Canadian Community Health Survey (2002) provided 12-month prevalence estimates of depression that are slightly lower than those found in the US at 4.8% (Canadian

[1] For the Global Burden of Disease studies, two important measures of disease burden were developed; Disability-Adjusted Life Years (DALYs) and Years Lived with Disability (YLD) (Murray and Lopez, 1996) , both of which have since become widely employed in the health literature. DALYs measure the burden of disease by combining estimates for years of life lost due to early mortality from a particular disease and years lived in disability. In contrast, YLDs only consider years lived in disability.

Community Health Survey [CCHS], 2002). These measures of prevalence contribute to estimates suggesting that approximately 340 million people globally are impacted by depression (WHO, 2004).

Depression is a complex disorder with affective as well as cognitive, behavioural, and somatic symptoms (American Psychiatric Association [APA], 2000). The diagnosis of depression is based on the presence of a pattern of symptoms, because like most other mental disorders, depression does not have an identifiable pathophysiological basis. This has resulted in questions surrounding the validity and reliability of the diagnosis and complicated the analysis of treatment response (Horwitz, 2002). Primary symptoms associated with depression include: diminished interest and/or pleasure in daily activities, significant changes to weight and sleep pattern, overwhelming fatigue, poor concentration, feelings of worthlessness or excessive guilt, and persistent thoughts of death or suicide (APA, 2000). The consequences of these symptoms are considerable and impact the individual with the illness, as well as their family and friends (Maurin and Boyd, 1990). Further, the illness is associated with a significant societal burden related to health care costs and diminished productivity. In 1998, depression was estimated to result in $2.6 billion dollars in lost productivity (Statistics Canada, 2007). Further, depression is recognized as "one of the most work-disabling chronic conditions because of its impact on absenteeism and multiple dimensions of presenteeism"[2] (Myette, 2008, p. 483).

[2] Absenteeism (i.e., absence from work) is associated with lower levels of lost productivity than presenteeism (i.e., lost productivity which occurs when employees continue to work despite decreased level of function).

Current treatment approaches for depression most commonly involve the use of an antidepressant medication and less often psychotherapy (e.g., cognitive behavioural therapy, interpersonal therapy, etc.) or a combination of the two (Canadian Mental Health Association, 2010). Unfortunately, a recent study by Kirsch and colleagues (2008) showed that when published and unpublished clinical trial data are reviewed, the efficacy of antidepressant medications falls below that of clinical significance for patients with mild to moderate depression. This finding has rocked the mental health community, bringing into question what has been considered by many to be the cornerstone of treatment for depression. Other more novel approaches to depression treatment include supported self-management, electroconvulsive therapy, vagus nerve stimulation, and self-care strategies (e.g., excercise, good nutrition and sleep habits, etc.) (Institute of Health Economics, 2010), however the efficacy and availability of these approaches is still being established.

In an effort to better understand the potential for reducing the economic burden of derpression, Andrews and colleagues (2000) conducted a study which examined the effect sizes of a variety of treatment methods derived from best practices. Their findings allowed them to create a model of the burden potentially averted through changes to current practice. The authors found that optimal treatment leads to better health outcomes, while also costing almost four times less than current approaches. Of particular interest to researchers and policy makers looking to decrease the economic burden associated with depression are their findings that:

> ...13 percent of the burden of depression is currently being averted by specific treatment at a cost of some $37 000 per DALY gained. If a stepped care model that incorporates prevention, self-care, primary care and specialist care is implemented, the present budget would allow effective coverage to increase [from 32%] to 100%, the burden averted by specific treatment to increase to 36% and the efficiency to increase to $10 000 per DALY gained (p. 183).

Although the authors acknowledge that a number of assumptions had to be made in order to conduct the modelling exercise, their findings are persuasive and warrant further exploration.

Depression is a disabling disorder that has implications for the individual and their family, and has far-reaching social and economic consequences for society. Further, studies indicate that the prevalence of the disorder is increasing and affecting a large proportion of the global population. Given the burdens associated with depression, understanding *who* gets depression and *why* is crucial in order to design and implement appropriate interventions to address this important public health issue.

2.2 Social Determinants of Depression

Research and theory surrounding the causal mechanisms believed to operate in the development of depression come from the biological, psychological, and social sciences (Schwartz, 2006; Thoits, 2006). Biological explanations of depression include factors such as genetic endowment (i.e., inherited traits or characteristics) (Schwartz, 2006) and abnormal

neurotransmitter levels (e.g., the hypothesis that low levels of serotonin cause depressive symptomology) (Owens and Nemeroff, 1994). Theories surrounding the psychological basis of depression are diverse and are informed by underlying psychological model or theory. Psychological characteristics believed to be involved in the development or maintenance of depression include such factors as early life experiences that impact adult functioning and issues surrounding with the way people think about or perceive life events (Peterson, 2006). Much of the social sciences literature has focused on identifying the social determinants of depression which include: gender, socioeconomic status (SES), level of social support, marital status, and employment status, amongst others (Blazer et al., 1994; Brown, Bifulco, and Harris, 1987; Dohrenwend, 1990; Karasek and Theorell, 1990; Kessler et al., 2003; Lennon, 2006). Drawing from this extensive literature, I will focus on the social determinants of gender (Blazer et al., 1994; Kessler et al., 2003) and socioeconomic status (SES) and poverty (Dohrenwend, 1990), as these factors have been widely acknowledged consistently to be key mechanisms in the origins of depression. Prior to this overview of gender, SES, and depression, I will include a discussion surrounding the impact of exposure to stress (Brown, Bifulco, and Harris, 1987; Karasek and Theorell, 1990), as "underlying [these] social determinants...is the fundamental importance of stress as a contributory factor in health" (Vancouver Island Health Authority, 2006, p. 2).

2.2.1 Stress

The dominant relationship between stress and depression has appeared in the literature for many decades and focuses largely on two types of stress:

acute stressful life events and chronic stress (Brown, Bifulco, and Harris, 1987; Karasek and Theorell, 1990; Kessler, 1997; Turner, Wheaton, and Lloyd, 1995). Studies focusing on acute stressful life events (SLE) (e.g., divorce, widowhood, etc.) and depression consistently demonstrate a correlation between these stressors and the onset of depression, and also suggest a dose-response relationship between the severity of SLE experienced and development of depression (Kessler, 1997). Research on the link between chronic stress (e.g., chronic marital problems, long-term illness, chronic role-related stressors, low SES and poverty, etc.) and depression has emerged in the stress literature more recently and has been found to play an even greater role in the development of depression compared to experiences of SLE (Wheaton, 2006).

Unfortunately, experiences with one type of stress are often associated with exposure to subsequent stressors, a concept referred to as "stress proliferation" (Pearlin, 2006), potentially making vulnerable groups or populations increasingly vulnerable. Further, the stress research has also identified factors that mediate against negative mental health outcomes including: coping skills, social support, and mastery. However, these resources are not equally distributed amongst members of society. (Folkman and Lazarus, 1986; Pearlin, 2006).

2.2.2 Gender

Being a woman is one of the strongest predictors of depression. Not only has depression been identified as the leading cause of disease burden amongst women (WHO, 2008), but women are up to two times as likely to experience the

disorder as their male counterparts (Blazer et al., 1994; Kessler et al., 2003). In Canada, the 12-month prevalence of depression amongst women is 1.6 times greater than the prevalence amongst men (5.9% vs 3.7% respectively) (CCHS, 2002). While it has been argued by some that the gender differences in depression are simply the result of differential treatment-seeking patterns, symptom perception, and reporting between males and females (Phillips and Segal, 1969), there is a broad research literature highlighting factors related to depression that could account for the differential rates by gender. These factors include social and economic factors that are not only correlated with depression, but are much more common amongst women including: the stress associated with balancing household and employment responsibilities (Cleary and Mechanic, 1983; Haymann, 2000; Lennon, 2006; Rosenfield, 1980), experiences of sexual violence (Dienemann et al., 2000; Heim et al., 2000), and poverty or lower relative levels of socioeconomic status (SES) (Caiazza, Shaw and Werschkul, 2004; Mirowsky and Ross, 2006; Organization for Economic Cooperation and Development, 2010).

Additionally, research demonstrates that women and men are exposed to different types of stressors; and further, that they manifest this stress differently (Barnett et al., 1987). There are a number of different explanations for the gender differences in stress. Rosenfield's work on stress demonstrates that women tend to *internalize* negative feelings projecting them inwards- resulting in depression, while men *externalize* these feelings- manifesting as substance use disorders and aggressive behaviour (2006). Almeida and Kessler (1998) suggest that

women are more likely to end up in stressful circumstances than men, while others propose that differences in gender roles expose women to greater levels of daily stress (Kessler and McLeod, 1984) and that women have greater levels of exposure to chronic stress (McDonough and Walters, 2001; Turner et al., 1995). Furthermore, stressors such as sexual violence and discrimination related to sex are much more prevalent amongst women (Heim et al., 2000; Klonoff, Landrine, and Campbell, 2000).

2.2.3 Socioeconomic Status

While there is debate in the literature as to whether mental disorders lead to lower levels of SES (social-selection argument) or whether lower social class positions result in the development of mental disorders (social-causation argument) (Eaton and Muntaner, 2006), the inverse relationship between SES and depression has been demonstrated repeatedly (Dohrenwend, 1990; Dohrenwend et al., 1992; Lennon, Blome and English, 2002; Muntaner et al., 1998; Murphy et al., 1991). For example, researchers have found that SES (based on measures of material resources, standard of living, skills, and social relationships) is consistently associated with a higher prevalence of depression in cross-sectional studies and in select prospective cohort studies (Kessler et al., 1994; Lorant et al., 2005; Lorant et al., 2007).

Additionally, in a recent study employing data from Canada's National Population Health Survey, researchers found low levels of education (OR=1.86, 95% CI 1.28-2.69) and financial strain (OR=1.65, 95% CI 1.19-2.28) to be

associated with depression amongst the employed population (Wang, Schmitz, and Dewa, 2010).

Theories of stress and cumulative disadvantage have been used to explain the differential rates of depression based on SES indices. Drawing from this theory, low SES and poverty is viewed as a pathway to depression for many women, as these factors lead to greater levels of uncontrollable SLE and chronic stress, which in turn, lead to higher rates of depression (Belle and Doucet, 2003; Kessler, 1997). Further, not only are those with the lowest levels of income subject to the greatest cumulative burden of stress, but they often suffer from poor coping styles and have lower levels of social support, which frequently operate to attenuate the influence of stress (Ross and Wu, 1996; Turner and Lloyd, 1999; Turner, Wheaton, and Lloyd, 1995). Pearlin (2006) nicely highlights the differential burden of stress pointing out that "social and economic statuses may regulate the stressors to which people are likely to be exposed and their proliferation, the moderating and ameliorative resources to which they have access, and the ways in which they manifest disorder" (p. 175).

2.3 Treatment-Resistant Depression

Depression is a burdensome disorder that is disproportionately distributed amongst women, especially women of lower SES, often through experiences of stress. Unfortunately, despite a number of available treatments for depression, as many as 50- 70% of the population diagnosed with depression will not achieve symptom remission, and are described as experiencing treatment-resistant depression (TRD) (Greden, 2001). Although the research exploring the

associations between sociodemographic factors and TRD is limited, it is reasonable to expect that the key social determinants of depression including female gender and low SES or poverty and their relationship with stress are also linked to TRD. Further research in this area is needed in order to more effectively address this health problem.

2.3.1 What is TRD? The Elusive Definition

The literature on TRD is not without its problems, perhaps most significant are problems with the definition itself, which continues to elude researchers (Berlim and Turecki, 2007a; Berlim and Turecki, 2007b; Fava, 2003; Greden, 2001; Sackeim, 2001). In his work on TRD, Greden (2001) discusses the variation found in the literature surrounding the definition of TRD. He argues that remission should be the ultimate goal of treatment, and that absence of remission, should be used as criteria for determining the presence of TRD, a recommendation echoed by other researchers in the field (Berlim and Turecki, 2007a, Berlim and Turecki, 2007b). Berlim and Turecki (2007a; 2007b) have noted over 10 different definitions for TRD appearing in the specialized literature. However, through a systematic review of randomized trials for TRD (n=47), they report a general consensus within the literature which defines clinically significant TRD as "an episode of major depression [that] has not improved after at least two adequate trials of different classes of [antidepressants]" (n=26) (2007b, p. 703). The authors further argue that TRD should be viewed on a continuum ranging from partial response to complete treatment resistance as opposed to an "all-or-none" phenomenon (2007a, p.48). They point out that an inadequate

response to treatment should constitute a "failure to achieve remission" (2007b, p.704), and that future studies should employ this criteria as the "gold standard outcome" (2007b, p.704), a conclusion that parallels Greden's (2001) work.

Fava, a researcher based out of the Depression and Clinical Research Program at Massachusetts General Hospital and Harvard Medical School, defines TRD as a failure to achieve remission following an adequate trial of antidepressant therapy. This definition differs from that proposed by Berlim and Turecki (2007a; 2007b) in that it does not specify *two* adequate trials of antidepressant therapy. Like other TRD researchers (Berlim and Turecki, 2007a; Berlim and Turecki, 2007b; Greden, 2001), Fava stresses the importance of remission as the treatment goal. The researcher notes that individuals with residual depressive symptoms show "poorer outcome[s] and increased relapse risk" (p. 649), a finding supported by other research in the field (Fava, Fabbri, and Sonino, 2002; Judd et al., 1998; Kennedy and Paykel, 2004). Interestingly, Fava acknowledges the narrow definition currently used to define TRD, noting it to be "pharmaco-centric" (p. 655) and suggests the need to incorporate psychotherapy into the treatment approach for patients with TRD; however, this suggestion remains only that.

2.3.2 Disease and Economic Burdens of Treatment-Resistant Depression

Given the inconsistency in definition, it is difficult to accurately measure the prevalence or disease burden associated with TRD. However, despite the conceptual limitations, estimates of the burdens of TRD are believed to be substantial. Greden (2001) argues that the disease burden associated with TRD

is "unacceptably large" (p.30) and represents a significant public health issue requiring a "paradigm shift" (p.30) towards prevention, early intervention, and adequate treatment. Further, he maintains that if better prevention and control measures are not instituted, depression will move from the fourth leading cause of disease burden worldwide to the second (behind ischemic heart disease) by 2020. Unfortunately, following the last update of the Global Burden of Disease study, it is clear that this movement is already taking place as depression is currently estimated to be the third leading contributor to disease burden worldwide (WHO, 2008). Moreover, in light of the chronic nature off the illness, it is argued that TRD would result in the highest levels of disability related to depressive disorders (Greden, 2001).

Given the substantial posited prevalence and disability associated with TRD, it is reasonable to anticipate that the economic burden surrounding TRD would also be substantial. In a large study of US workers, the differential health care costs associated with depression and TRD was examined in comparison to a random sample of workers (Greenberg et al., 2004). Given the difficulties posed by the absence of universally recognized definitional criteria for TRD, the researchers designed a classification scale drawing from the treatment patterns described in the literature for individuals with TRD. This scale was used in order to classify individuals as TRD-likely and TRD-unlikely[3]. The results indicate that individuals classified as TRD-likely used "significantly more healthcare resources,

[3] Greenberg and colleagues designed a classification scale which employed an algorithm characteristic of the treatment pattern described in the literature for individuals with TRD. This algorithm was used to classify their depressed sample as TRD-likely and TRD-unlikely.

had significantly more claims for diseases of different body systems, and had significantly higher direct and indirect expenditures than employees classified as TRD-unlikely" (Greenberg et al., 2004, p.372). Further, costs associated with TRD-likely employees were more than double that of TRD-unlikely employees and almost quadruple that of employees from the random sample. Given these substantial differences in health care costs, the authors conclude that significant savings could be achieved through "timely and effective treatment of TRD employees" (Greenberg et al., 2004, p. 372).

2.3.3 Risk Factors Associated with Treatment-Resistant Depression

While research evidence indicates a significant economic burden associated with TRD, little is known about *who* is most likely to experience the disorder or the specific risk factors which likely influence the course of the illness. What little is known surrounds select sociodemographic factors including: limited social support (Bosworth et al., 2002), rural area of residence (Viinamaki et al., 2006), feeling unwanted during childhood (Ehnvall et al., 2005), greater exposure to negative life events (Amital et al., 2008), job loss and financial stress (Amital et al., 2008), and in some studies, female gender (Simpson, Nee, and Endicott, 2007). Additionally, a number of psychiatric and medical comorbidities have been identified as risk factors including: anxiety (Brown et al., 1996), personality disorders (Reich, 1990; Viinamaki et al., 2006), psychotic depression (Schatzberg and Rothschild, 1992), substance use (Worthington et al., 1996), and arthritis and circulatory problems (Oslin et al., 2002). While all have been related to TRD, the research in this area should be taken cautiously as it is

plagued by inconsistent findings (Fava, 2003). More work in this area is necessary in order to better identify, prevent, and treat individuals or populations vulnerable to TRD.

3: METHODOLOGY

3.1 Scoping Review of Treatment-Resistant Depression Literature

In an effort to better understand what is currently being done to address this debilitating and burdensome illness, a scoping review was conducted. Scoping reviews are a newer research methodology that has emerged to assist researchers in quickly and systematically identifying the breadth of literature in a research area. Scoping reviews can be contrasted with systematic reviews in that they are aimed at illuminating the *scope* or extent of literature in a particular area, whereas the former are narrower in their focus and seek to answer particular research questions from the available literature, while also encompassing a component to identify the quality of research included. Arksey and O'Malley (2005) describe scoping reviews as having at least four potential functions: to map the current state of literature in an area of interest, to determine the usefulness or feasibility of conducting a systematic review, to summarize and disseminate research findings to an audience (e.g., policy makers, consumers, etc.), and finally, to identify gaps or areas where further research is required. The York scoping review framework created by Arksey and O'Malley (2005) identifies five essential steps for conducting a scoping review: 1) identification of the research question, 2) identification of relevant studies, 3) selection of studies, 4) charting of data, and 5) collating, summarizing, and reporting results. This

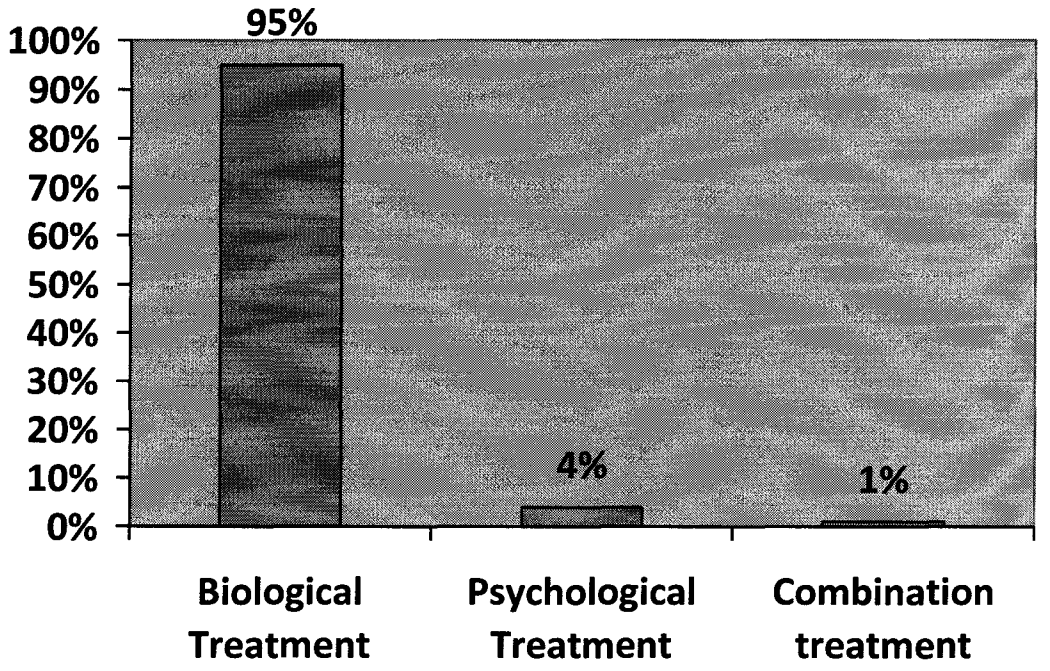
scoping review utilized the York framework to survey the literature and illuminate the current state of evidence surrounding treatment paradigms for TRD, as well as identify gaps in the literature and treatment approach.

A systematic search of the literature was undertaken utilizing six electronic databases (Academic Search Premier, CINAHL, Medline, PsycArticles, PsychInfo, and Health Source). Keywords to identify literature related to treatment-resistant depression included: "treatment-resistant" AND "depression", "refractory AND depression", "therapy-resistant AND depression", "treatment-resistant AND depression AND social", "treatment-resistant AND depression AND nonpharmacological", "treatment-resistant AND depression AND novel", "medication-resistant AND depression", "treatment-resistant AND depression AND burden", "treatment-resistant AND depression AND public health". Resulting titles (n= 2392) were scanned to identify articles that met the inclusion criteria which included: research articles related to unipolar TRD treatment amongst the adult population (ages 18 and 65) with English language abstracts available, and publication dates from 2005-2010. Letters to the editor and responses to articles were excluded. The remaining 245 articles were exported to reference management database, Mendeley. These studies were then examined in greater detail, and the data charted by theme (see Appendix A for reference lists by treatment paradigm). These themes inform the structure of the following results.

4: RESULTS

The literature identified through the scoping review can be classified thematically by underlying treatment paradigm as biological (n= 229), psychological (n=11), or combination therapy (i.e., biological and psychological therapies used simultaneously) (n=5), with none of the literature falling within a social paradigm (see Figure 1.0 for visual representation of the magnitude of research stemming from each paradigm). The following discussion is presented in order of the weight of literature falling within each theme.

Figure 1- Magnitude of Research Stemming from each Paradigm



4.1 Biological Therapies

Of the articles identified, 95 % (n=229) fell under the biological treatment paradigm (i.e., treatment targeting the pathophysiology believed to cause the disorder), which has been the dominant approach to mental illnesses for the last several decades (Schwartz, 2006). The literature in this theme was further classified by intervention as: pharmacotherapy (n=137), repetitive transcranial magnetic stimulation (rTMS) (n=33), vagus nerve stimulation (VNS) (n=26), deep brain stimulation (DBS) (n=16), electroconvulsive therapy (ECT) (n=13), and

neurosurgery (n=4) (see table 1.0 for synopsis of the number of articles by treatment paradigm).

The most dominant treatment approach emerging from the literature on TRD is psychopharmacology. Many of the articles represent the findings from the Sequenced Treatment Alternatives to Depression (STAR*D) trials, a large National Institute of Mental Health (NIMH) funded study undertaken to identify the efficacy of different treatment approaches for people who have not achieved satisfactory response from initial antidepressant treatment (NIMH, 2010).

The psychopharmacology literature focuses largely on determining efficacious augmentation strategies for those who have not achieved remission following antidepressant monotherapy. Augmentation is a common approach employed in the treatment of TRD and is endorsed by various TRD treatment staging models including the: Thase and Rush Model of Staging Treatment Resistance, The Massachusetts General Hospital Staging Method, and The European Staging Method (Berlim and Turecki, 2007a; Fava, 2003). While many of the articles provide reviews or discussions surrounding augmentation strategies, others provided evidence of the efficacy of specific augmentation combinations. The types of medications studied for use in augmentation therapy of TRD include: mood stabilizers (e.g., lithium, lamotrigine), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), thyroid hormones (e.g., T3, testosterone), vitamin supplements (e.g., zinc), antipsychotics (e.g., quetiapine, olanzapine, risperidone), nicotinic antagonists, antibiotics (e.g., D-cycloserine),

psychostimulants (e.g., methylphenidate), opiates, (e.g., buprenorphine), and anaesthetics (e.g., ketamine).

Like the pharmacotherapy literature, much of the literature on other biological therapies focuses on determining the efficacy of a specific treatment, or combinations of treatments. The efficacy literature conducted on rTMS reports primarily promising results. While the remaining research exploring this therapy took a more micro level approach, in an effort to identify certain physiological changes associated with the treatment.

Similarly, the studies on VNS, DBS, ECT, and neurosurgery were largely focused on determining the safety and efficacy of these treatment approaches. Many of these studies also looked at the efficacy of combining these treatments with each other (e.g., VNS combined with ECT). More research in the area of relatively novel treatment is necessary as many of the studies demonstrated inconsistent outcomes, had small sample sizes, or require longer follow-up periods.

4.2 Psychological Therapies

Approximately 4% (n=11) of the articles identified through the scoping review could be classified as stemming from a psychological paradigm (i.e., treatment addressing the behaviour, emotion, or thought patterns believed to cause the disorder). This literature consisted largely of studies exploring the application of cognitive behavioural therapy (CBT) in the treatment of TRD (n=7). However, there is a limited literature on more novel psychological approaches

including mindfulness and dialectical behavioural therapy (DBT). Many of the articles falling into this theme are discussion papers as opposed to empirical studies. However, the limited literature that does provide data on the efficacy of psychotherapy shows incongruent results. Clearly, given the relatively minute set of studies conducted, further research is needed in this area.

4.3 Combination Therapies

In addition to the literature that could be clearly classified as biological or psychological in paradigm, there was also a very limited research exploring a combination of these approaches (n=5). Overall, this literature indicates that utilizing a combination of biological and psychological approaches results in superior treatment outcomes.

4.4 Social Interventions

Interestingly, despite the considerable research demonstrating the social determinants of depression, none of the articles identified through this scoping review of the TRD literature addresses these factors.

Table 1- Number of Articles by Treatment Paradigm

Treatment/Therapy	# of articles identified
	Biological Paradigm
Pharmacotherapy	137
Repetitive transcranial magnetic stimulation	33
Vagus nerve stimulation	26
Deep brain stimulation	16
Electroconvulsive therapy	13
Neurosurgery	4
	Psychological Paradigm
Cognitive Behavioural Therapy	7
Mindfulness therapy	2
Dialectical behavioural therapy	1
Other	1
	Combination
Pharmacotherapy + psychotherapy	5
	Social Paradigm
N/A	0
All therapies	**245**

5: DISCUSSION

Depression is a complex and disabling disorder that is disproportionately experienced by women, people of low SES, and those experiencing acute and chronic stressors. Further, a large proportion of the population seeking treatment for depression does not respond adequately to current treatment approaches, with up to 70% coming to be seen as treatment-resistant (Greden, 2001). The high prevalence of TRD is responsible for substantial health, societal, and economic burdens. In fact, because of the chronic nature of the disorder, TRD is posited to result in the greatest burdens associated with depressive disorders (Greden, 2001). Given the high prevalence, significant burdens, and the failure of current treatment approaches, TRD represents a significant public health issue requiring action. This study aimed to identify the current state of research on the treatment approaches to TRD as a means of synthesizing the literature in this area and identifying knowledge gaps. It is hoped that this information may be utilized in an effort to influence policy and practice, and stimulate needed change to improve health outcomes for this population.

5.1 Study Implications

Perhaps the most startling finding from this review, is the sheer lack of evidence surrounding TRD and supporting its prevention and treatment. Although we know that TRD is highly prevalent amongst the population experiencing depression, we are missing critical research to allow us to better

address the disorder. One of the issues leading to this difficulty is the lack of a universally accepted definition for TRD. As a result, we do not have accurate measurements of the prevalence and associated burdens of the disorder. This represents a significant barrier to our ability to effectively address this important public health issue. Additionally, we are lacking the epidemiological evidence necessary to understand *who* is at risk for TRD so that appropriate interventions can be established. This should be of significant concern to policy makers, researchers, health professionals, and the general public. Without a better understanding of the disorder, the prevalence is likely to continue to grow as are the associated health, social, and economic burdens. More research surrounding this disorder is necessary if we hope to make progress in reducing the incidence and prevalence of TRD.

In addition to the alarming gaps in research evidence surrounding TRD, the findings of this scoping review also highlight issues stemming from the narrow scope of current research. Despite acknowledgement that "depression is the product of a complex interaction between biological, psychological and social elements" (Patten and Juby, 2008, p. 5), the proposed definitions for TRD, treatment staging models employed, treatment approaches utilized, and research conducted remains overwhelmingly biological in orientation (Berlim and Turecki, 2007a; 2007b; Fava, 2003).

As discussed earlier, one of the primary issues surrounding the work on TRD is the lack of a universally accepted definition of the illness. The absence of a consistent definition of TRD has been problematic in the literature in that it has

lead to difficulties in accurately and consistently measuring related constructs. However, this flaw may actually serve as an opportunity for researchers, clinicians, and policy makers to come together in an effort to create necessary change. Efforts to expand the definition of TRD to more accurately reflect the experience and to capture therapies beyond the biological paradigm are needed.

In addition to problems with the lack of research evidence and the inconsistent and narrow definitions proposed for TRD, there are also issues surrounding the detrimentally narrow focus within the treatment staging models employed. Fava (2003) acknowledges the "pharmaco-centric" approach to TRD, and the need to incorporate other evidence-based therapies, including psychotherapy, into the depression treatment approach. However, despite this claim, psychotherapy does not appear in the Massachusetts General Hospital Staging Method to classify TRD which was developed by Fava and colleagues, or The European Staging Method, or the Thase and Rush Model of Staging Treatment Resistance. Future research and practice guidelines must acknowledge the important role of non-pharmacologic interventions in the treatment of depression, and incorporate these approaches into a universally accepted diagnostic definition and treatment algorithm for TRD.

Given our understanding of the multi-faceted causal mechanisms underlying depression and its treatment-resistant counterpart, one could hypothesize that the most effective treatment approaches for depression would be equally complex and include interventions that address each of the factors known to contribute to this debilitating disorder. Interestingly, interdisciplinary

and multimodal approaches to TRD remain novel. For example, although psychotherapy has been established in the clinical guidelines literature as an effective and evidence-based treatment for depression (Canadian Psychiatric Association, 2001), psychological approaches to the treatment of TRD are extremely limited. Efforts to enhance access to this approach are necessary. In the Canadian context, the Canada Health Act provides citizens access to universal health care coverage, which includes all "medically-necessary" hospital and physician services (Health Canada, 2010). However, this leaves many Canadians, especially those who are already more vulnerable to depression due to SES or employment status, with limited access to psychological services (as they are not considered *medically necessary*). Further, Canadians who are the bearers of extended health coverage (often provided through place of employment) are limited to extremely low levels of annual reimbursement for psychological services, likely to the extent that these interventions would be sub-therapeutic. Political action and the development of creative treatment options are necessary in order to generate more affordable psychotherapy, and thus, promote equitable access to this important treatment modality.

The proposed definitions and interventions for TRD represent a "downstream approach"- seeking to address the problem once it is already wreaking havoc. The downstream approach is common in health care, but is not necessarily the most effective strategy in reducing incidence and prevalence of disorder. With the growing prevalence of depression and TRD and the resulting burdens, research identifying appropriate "upstream approaches" is needed.

Upstream approaches to health target the root causes of the issue and help to prevent incidence of illness. Research identifying the various factors contributing to the disorder is necessary. This would allow for interventions and policies that address the social determinants of depression, foster mental health, and prevent poor living conditions. One could imagine that if members of the TRD population are experiencing adverse living situations related to SES (e.g., poor working conditions, unemployment, low levels of education, etc.), gender (e.g., violence, stress related to competing life roles, sexism, etc.), or stress (e.g., loss of a loved one, financial insecurity, etc.) that popping a pill or being zapped by electricity is not going to be all that effective in relieving their depressive symptoms within this difficult context.

5.2 Barriers to a Paradigm Shift

Unfortunately, broadening the scope of research surrounding TRD will not be easy. There are powerful influences operating to maintain the narrow approach to TRD, including the pharmaceutical industry. For example, research identifies strong ties between those creating clinical practice guidelines and the pharmaceutical industry (Choudhry et al., 2002), a factor which may have contributed to the biological focus of the TRD treatment staging models. Additionally, there exists a publication bias, as is evidenced by the work of Kirsch et al. (2008) that can (and has) lead to a distorted view of the efficacy of pharmacological treatment options. This bias is one that clearly benefits the pharmaceutical industry, and not patient care. Further, given that the diagnosis of depression itself is based on a set of relatively subjective symptoms, as opposed

to a quantifiable test or examination, claims have been made that drug companies exploit this factor in order to market and sell more drugs (Moncrieff et al., 2005). This practice is critiqued for medicalising social and personal concerns and turning the social construction of illness into a "corporate construction of disease" (Moyihan et al., 2002, p.886). Through elaborate marketing campaigns, the pharmaceutical approach has become entrenched in our culture influencing consumer expectation and prescriber practices (Moyihan et al., 2002). Efforts to expand the clinical treatment staging models and overhaul the proposed definitions of TRD are necessary in order to acknowledge and address the important social and psychological roots of the disorder and improve health outcomes.

5.3 Limitations

This work should to be considered in light of its limitations. Specifically, there are limitations surrounding the scoping review methodology. Scoping reviews are a useful tool for surveying the literature surrounding a topic. However, scoping reviews do not address or provide definitive answers to research questions. Additionally, given the lack of research surrounding the causal factors associated with TRD, speculations had to be made that these factors would be similar to the ones underlying depression, including: gender, low SES, and the influence of stress. Further, the lack of a universally accepted definition of TRD makes studying the disorder tricky and leads to difficulties in accurately measuring the disease burden associated with the illness. The narrow, biological focus currently employed ignores many of the key causal

mechanisms that underlie TRD. More research in this area is required if we are to begin to effectively address this important public health issue.

6: CONCLUSIONS

Depression is a complex disorder associated with significant health, social, and economic burdens. Current treatment approaches are not effective in producing remission in a large proportion of those affected by this illness, resulting in a high prevalence of TRD, a form of depression which is posited to result in even greater disease burden. However, despite our knowledge that depression (and TRD) results from the interaction of biological, psychological, and social factors, our approach to TRD is detrimentally narrow, with little research covering the psychological or social realms of the disorder. This scoping review highlights the narrow focus currently associated with TRD treatment, but perhaps more importantly, identifies the significant gaps in our knowledge surrounding the epidemiology and risk factors associated with the disorder. Thus, a paradigm shift in treatment approach should be considered premature, as we do not currently have the evidence necessary to support this change. Efforts to expand the scope of research are necessary if we hope to decrease the substantial burdens associated with TRD and to promote the health of our population.

APPENDICES

Appendix A

Biological Approaches

Pharmacotherapy

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