Treatment of Dysthymic Disorder in Older Adults

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Dedication

This scholarly project is dedicated to my mom, dad, and two sisters Renee and Catherine. Without their love and support, I would not be where I am today.

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Introduction

Depression affects approximately 121 million individuals and is the leading cause of disability worldwide (World Health Organization, 2008). A chronic form of depression known as dysthymia can be especially debilitating. The Diagnostic and Statistical Manual of Mental Disorders Fourth Edition Text Revision (DSM-IV-TR) defines dysthymic disorder (DD) as a "depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least two years" (*DSM-IV-TR*, 2000). In addition to a depressed mood, an individual must have two or more of the following symptoms: poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration or difficulty making decisions, and/or feelings of hopelessness.

Major depressive disorder (MDD), perhaps a better known form of depression, shares several diagnostic criteria with DD including insomnia/hypersomnia, fatigue or loss of energy, and inability to concentrate (*DSM-IV-TR*, 2000). Other criteria are unique to one disorder or the other. Diagnostic criteria specific to MDD include anhedonia and psychomotor agitation ("Dysthymia," 2005; Pier, Hulstijn, & Sabbe, 2004), while the presence of low self-esteem is a criterion specific to DD. MDD and DD also differ in symptom intensity and chronicity. In MDD, symptom intensity often varies from moderate to severe; symptoms must be present for at least two weeks and indicate a change in functioning for an individual. Patients with MDD often report interpersonal problems, but these problems either disappear or are seen as less problematic once the depression lifts. In DD, symptoms can vary from mild to moderate in intensity and are present for a much lengthier period of time, indicating a characteristic way of interacting with the world. Individuals with DD often report chronic interpersonal problems. In some cases, an

individual may meet criteria for both MDD and DD, and this is sometimes referred to as double depression.

Although sometimes thought of as a milder form of depression, dysthymia can cause significant and even greater suffering than MDD. In fact, dysthymic disorder, with and without concurrent major depression, is associated with greater impairment in social, physical, and role functioning than MDD alone (Spitzer et al., 1995). For example, dysthymic disorder can interfere with one's ability to maintain satisfying interpersonal relationships over an extended period of time. As a result of its chronic nature, DD may be associated with more days of missed work and has been shown to be associated with greater use of mental health services than MDD (Kessler et al., 1999; McFarland & Klein, 2005). Patients with DD consume a significant amount of healthcare resources and generate high costs due to doctor visits, laboratory tests, diagnostic procedures, hospital admissions, and pharmaceuticals. According to a multi-center, two-year longitudinal study, psychiatric and medical costs associated with care of the dysthymic patient are, on average, over $1000 per year (Barbui, Motterlini, & Garattini, 2006).

Early and Late Onset Dysthymia

Dysthymic disorder may be further classified as early or late onset dysthymia. According to DSM-IV-TR (2000), early onset dysthymia begins before age 21, and late onset dysthymia begins at 21 years of age or later. This age distinction is not universally accepted however. The ICD-10 code for early onset dysthymia is used to classify onset before the age of 30, while the code for late onset dysthymia describes onset between the ages of 30 and 50 (Barzega, Maina, Venturello, & Bogetto, 2001). Others have also described a unique form of dysthymia that occurs in individuals over the age of sixty (Devanand et al., 1994). Genetics, neurochemical imbalances (serotonin, norepinephrine, and dopamine), stress, and social isolation appear to play

a role in the development dysthymia regardless of age at onset ("Dysthymia," 2005); however, certain associated characteristics differ based on when the individual first experiences symptoms.

Barzega et al. (2001) report onset of dysthymia before age 21 to be associated with atypical symptoms including leaden paralysis (heavy sensation within the extremities) and hypersensitivity to interpersonal rejection. Onset before age 21 is also associated with female gender; high rate of double depression; and high prevalence of additional mental health conditions, developmental and learning disabilities, and personality disorders. In contrast, Devanand et al. (1994) found an equal gender distribution, predominance of pure dysthymia rather than double depression, a rare occurrence of personality disorders, and high frequency of life stressors preceding the onset of dysthymia among a group of research participants ≥ 60 years old. Risk factors associated with late onset dysthymia include medical illness, physical disability, cognitive deficits, and recent loss of a loved one (Devanand et al., 1994; "Dysthymia," 2005). Hypertension and heart disease are among the most common medical illnesses reported by those with late onset dysthymic disorder (Bellino, Patria, Ziero, Rocca, & Bogetto, 2001; Devanand et al., 1994). Although presentation of this disorder tends to vary with age of onset, symptom severity, degree of social impairment, and response to treatment do not differ (Barzega et al., 2001; Kocsis, 1998). Nevertheless, patients with early onset dysthymia are more likely to receive therapeutic intervention such as pharmacotherapy, psychotherapy, or combined pharmacotherapy and psychotherapy (Barzega et al., 2001).

Diagnosis of Dysthymia

Making the diagnosis of dysthymia is not always straightforward. It can be complicated by factors associated with patients, healthcare providers, and/or the healthcare system (Docherty, 1997). Barriers to diagnosis related to patients include a lack of personal awareness of

depression as a treatable medical illness, complaints of physical symptoms that dominate mental awareness, and shame which may prevent seeking help. In addition, some patients do not mention their symptoms because such symptoms have, for them, become the norm throughout the course of their chronic condition. Diagnostic impediments related to physicians include lack of training in problem recognition and treatment (Docherty, 1997). System-related barriers include limited coverage of mental health services, meaning that the psychiatric needs of patients are not assessed. The need for referrals in order to access mental health services creates administrative barriers as well. Reimbursement issues result in uncompensated services which are less likely to be provided. One additional system-related barrier to the diagnosis of dysthymia is the limited time spent with each patient—the reality associated with a health system where productivity is rewarded.

Diagnosis of dysthymia can be especially problematic in the elderly population. In addition to the factors listed above, three elements of aging can interfere with symptom recognition: comorbidities, cognitive impairment, and recent adverse life events (Bellino, Bogetto, Vaschetto, Ziero, & Ravizza, 2000). In a study performed by Devanand et al (1994), 52% of patients aged 60 or older with dysthymia reported a concomitant major medical illness. The high prevalence of coexisting medical conditions may create a medical bias where physician focus is on a patient's physical rather than psychiatric symptoms. Patients themselves might disregard feelings of depression and hopelessness as a normal response to their medical conditions and/or their getting older.

Cognitive impairment may also interfere with diagnostic accuracy among older adults. Cognitive deficits increase with age and have been shown to be more prevalent among elderly patients with dysthymia than among elderly individuals with a diagnosis of major depressive

disorder (Forsell, Jorm, & Winblad, 1994). Older patients with cognitive impairment may be unable to comprehend and appropriately respond to a provider's questions regarding their symptoms (Bellino et al., 2000). In order to take one's cognitive abilities into consideration throughout the diagnostic interview, a cognitive evaluation should precede and inform the approach to any older patient likely to be suffering from DD.

In addition, recent adverse life events, such as the loss of jobs, money, homes, functional capacity, friends, family, and independence can contribute to demoralization and be linked to the onset of dysthymia among older adults (Bellino et al., 2000). Once again, this patient population and their physicians may see the onset of prolonged depression in relation to recent losses as normal. Therefore, treatment of chronic depression may not be viewed as a priority. An understanding of normal versus abnormal grief reactions can help both the patient and provider recognize problematic responses to loss which may contribute to the onset of dysthymia.

Prognosis

Approximately two-thirds of all patients with DD will remain symptomatic for ten years or more, and only one in four will completely recover (De Lima & Hotopf, 2003; Kaplan & Sadock, 1996). Among primary care patients, only 11% who are diagnosed with DD receive adequate treatment in terms of duration and dose of pharmacotherapy and/or psychotherapy (Katon, von Korff, Lin, Bush, & Ormel, 1992). Poor treatment adherence and settling for partial response may also contribute to the poor prognosis of dysthymia (Reynolds, Alexopoulos, Katz, & Lebowitz, 2001). Dysthymia, particularly in the geriatric population, is associated with lengthy recovery and frequent relapse (Subramaniam & Mitchell, 2005). Improving the identification and treatment of DD will serve to enhance the quality of life of a large number of older adults.

Problem Statement

Approximately 2% of individuals over the age of 60 suffer from dysthymia (Blazer, 1987). While the percentage of older adults with DD may or may not change over the next few years, the sheer number of those suffering from this condition will increase dramatically in the near future. The U.S. Census Bureau has projected that the number of Americans over the age of 65 will more than double between 2000 and 2010 (U.S. Census Bureau, 2004). Understanding dysthymia in older adults is essential not only because of an increase in the number of older patients with this condition, but also because of the serious consequences of dysthymic disorder. Dysthymia has been associated with medical illness, physical disability, cognitive decline, decreased quality of life, increased suicide, and increased all-cause mortality (Unutzer, Katon, Sullivan, & Miranda, 1999). Male gender, smoking, low educational level, polypharmacy, physical disability, and a decline in functional capacity are all predictors of mortality in elderly patients with DD (Bellino et al., 2000). Such findings do not indicate that organic features of dysthymic disorder directly impact mortality, but they do suggest that associated diseases and disabilities in those with dysthymia may increase overall mortality rates (Bellino et al., 2000).

While MDD is frequently studied, DD is not—particularly in older adults. Much of the current literature on the treatment of dysthymia reports on a broad cross-section of patients. In order to obtain a true appreciation of the implications of age on treatment of dysthymia, one must analyze research targeting individuals of advanced age. However, the paucity of this research requires one to critically review what is known about dysthymia in general and to identify factors that may or may not be applicable to older adults.

Scope

This scholarly project will serve as a qualitative review of treatment options currently available for dysthymic disorder in older adults. The phrase older adult will apply to individuals ≥60 years old throughout this text. Five published studies regarding pharmacotherapy in older adults and 3 comprehensive reviews of pharmacotherapy for dysthymia in the general population will be discussed. While no studies were located regarding psychotherapy of dysthymia exclusively in older adults, 2 studies regarding this treatment option across adult age groups are included. One study regarding pharmacotherapy versus psychotherapy in individuals over the age of 60, as well as 2 additional studies regarding pharmacotherapy versus psychotherapy in the general population are included as well. There were no studies located regarding combination therapy exclusively for older patients with dysthymia. Therefore, 3 studies regarding combination therapy across adult age groups are reviewed. All participants of the trials included in this review received a DSM-III or IV diagnosis of dysthymia via interview or psychometric testing. Studies that examined major depression, double depression, or did not make a distinction between forms of chronic depression were excluded. Double depression, in particular, was excluded due to the low incidence of this dual diagnosis among older adults.

Pharmacotherapy

Current treatment for dysthymia includes pharmacotherapy, psychotherapy, or combination therapy. The goal of pharmacotherapy is correction of biochemical deficiencies believed to be associated with dysthymic disorder. In the past, tricyclic antidepressants (TCAs) were the first line treatment for depressive conditions, including DD (Zisook & Downs, 1998). Although highly effective in the treatment of severe depression, TCAs have many adverse effects due to their high affinity for histaminic, cholinergic, and adrenergic receptors. Unfortunately, older adults are particularly vulnerable to these adverse effects. Antihistaminic reactions include weight gain and sedation, while dry mouth, blurry vision, urinary retention, constipation, and aggravation of glaucoma are attributed to anti-cholinergic effects (Zisook & Downs, 1998). TCA affinity for cholinergic receptors can also lead to memory disturbances. Perhaps most troublesome among older adults, is the orthostatic hypotension and reflex tachycardia which result from TCA affinity for alpha adrenergic receptors. Other dangerous cardiovascular effects include decreased heart rate variability, slowed cardiac conduction, and orthostasis. For these reasons, TCAs are contraindicated in those recovering from an acute MI and should be used with caution in those with a history of cardiovascular disease. Use of secondary amine TCAs, instead of the traditional tertiary amine TCAs, has shown decreased side effects, but cardiovascular side effects are still common among elderly patients taking these drugs (Zisook & Downs, 1998).

Monoamine oxidase inhibitors (MAOIs) are another class of antidepressants that have been used to treat DD in the past. This particular class of drugs has proven effective in the treatment of mood disorders such as major depressive disorder, dysthymia, and atypical depression (Zisook & Downs, 1998). MAOIs, however, may cause anxiety, agitation, insomnia, sedation, palpitations, and tachycardia. The adverse effect most prevalent and of particular

concern in older adults is orthostatic hypotension (Zisook & Downs, 1998). MAOIs are rarely used in this patient population due to these side effects, as well as their interaction with indirect sympathomimetic medications, selective serotonin reuptake inhibitors, and foods/beverages with concentrated tyramine. MAOIs can lead to hypertensive crises when used in combination with sympathomimetic agents and can cause serotonin syndrome when used with SSRIs.

Recently, dysfunction of the serotonergic neurotransmitter systems has been implicated in the development of DD (Bellino et al., 2000). Research on this system has led to the emergence of selective serotonin reuptake inhibitors (SSRIs). SSRIs have shown significant improvement over TCAs in regards to adverse effect profile and simplicity of dosage regimen—two factors especially important in older adults (Zisook & Downs, 1998). In addition, SSRIs, unlike other drugs used to treat depression, do not require blood concentration monitoring or electrocardiogram analysis prior to initiation of therapy (Reynolds et al., 2001). Furthermore, this class of drugs has proven just as effective as TCAs in the treatment of depression, except perhaps in some cases of severe depression. Side effects most common with the SSRIs include anxiety, insomnia, gastrointestinal distress, headaches, and sexual dysfunction. SSRIs also inhibit cytochrome P450 enzymes which are important for the metabolism of many other drugs including TCAs, antiarrhythmics, antipsychotics, beta blockers, calcium channel blockers, dextromethorphan, and codeine (Raj, 2004; Zisook & Downs, 1998). Therefore, a review of one's current medication list, checking for possible drug-drug interactions is crucial before initiating an SSRI.

Pharmacotherapy in the Older Adult

Fluoxetine (Prozac) is the longest acting SSRI with an elimination half life of 48-96 hours. A longer half life means fewer withdrawal symptoms and minimal physiologic effects

after a missed dose, but is also associated with prolonged side effects and drug interactions after fluoxetine discontinuation. Two studies examined fluoxetine in an older adult population with DD. Nobler and colleagues (1996) conducted a 13-week study that included 23 individuals 60 or older with a DSM-III-TR diagnosis of pure dysthymia. The mean duration of the current depressive episode among those chosen to participate was 18.5 +/- 17.1 years. The dose of fluoxetine administered throughout the study ranged from 20 to 60 mg/day, with a mean dose of 35.5 mg/day. Response criteria were as follows: 50% reduction in Hamilton Rating Scale for Depression (HAM-D) score from baseline, final HAM-D score ≤ 8, and Clinical Global Impression (CGI) score of 1 or 2. Using these criteria, 12 of 20 (60%) study completers were labeled as responders. The Treatment Emergent Symptom Scale (TESS) was used to assess the adverse effects of fluoxetine. The mean total TESS score did not change from baseline to study completion. Furthermore, there were no major complications related to drug therapy throughout the 13-week study. Limitations of this study include small sample size and lack of a control group. Exclusion criteria included cognitive dysfunction. This exclusion criterion limits application of these study findings to individuals with a Mini Mental Status Exam score of greater than twenty-four.

The second study of fluoxetine in older adults demonstrated a more limited effect for this SSRI. This study was a 12-week randomized, double-blind, placebo-controlled trial that enrolled 91 adults ≥60 years of age (Devanand et al., 2005). The mean end-point dose of fluoxetine given to those in the treatment group was 45.5 mg/day with a dosage range of 20-60 mg/day. Responders were classified as those who achieved a 50% reduction in HAM-D scores from baseline and a CGI improvement score of 1 or 2 at study completion. According to these criteria, 37.5% of study completers treated with fluoxetine and 23.1% of those treated with

placebo were responders. The researchers concluded that individuals receiving fluoxetine showed modestly greater improvement than those receiving placebo. The Treatment Emergent Symptom Scale (TESS) found yawning, which was more common in the fluoxetine group, to be the only side effect that differed significantly between groups.

This study design showed methodological improvement over the open label trial of fluoxetine performed by Nobler et al. (1996) in that it was randomized and placebo-controlled. However, Devanand et al. also excluded patients with impaired cognition and dementia. Other study characteristics further limit generalizability. White males constituted the large majority of study participants. Furthermore some participants were recruited by advertisement and were therefore self-referred. As a group, self-referred patients may respond better or worse to pharmacotherapy than the average person with dysthymia. Better response may be a result of greater motivation and hope for recovery, while worse response could accompany longer illness duration among this self-referred group.

The effectiveness of another SSRI, sertraline (Zoloft), was compared to amisulpride, a substituted benzamide, in a trial of 49 adults over the age of 65 with dysthymia (Bellino et al., 1997). Twenty-six patients were treated with sertraline 50 mg/day, and 23 patients were treated with amisulpride 50 mg/day. Treatment duration was six months. Nine participants did not complete the study. Five individuals (4 receiving sertraline and 1 receiving amisulpride) withdrew due to adverse effects, and 2 participants in each group were excluded as a result of non-compliance. Response was defined as a 50% or greater reduction in Hamilton Rating Scale for Depression (HAM-D), Hamilton Anxiety Rating Scale (HARS), and/or Brink's Geriatric Depression Scale (GDS) scores. The only scale that indicated a significant difference in percent responders at three months was the HAM-D. Determination of percent responders using this

scale labeled 74% of those patients taking amisulpride and 38% of those patients taking sertraline as responders. None of the scales used to determine percent responders indicated an advantage for one drug over the other at six month follow-up. Furthermore, there did not appear to be a statistically significant difference between the sertraline and amisulpride groups in regards to number of drop outs or number of participants reporting adverse events. Both drugs were generally well-tolerated by study participants.

Other recent studies have linked norepinephrine deficiencies with the onset of depressive conditions such as MDD and DD (Bellino et al., 2000). Selective norepinephrine reuptake inhibitors (SNRIs) have therefore emerged as an additional treatment option for those suffering from dysthymia. SNRIs, like SSRIs, have a minimal adverse effect profile. Histaminic, anticholinergic, and adrenergic side effects are minimal, and the cardiac profile is relatively benign. In addition, sexual side effects are less frequent than they are with the SSRIs. Venlafaxine (Effexor, Effexor ER) is both an SSRI and SNRI. At doses less than 150 mg, venlafaxine functions primarily as an SSRI, but as the dose administered exceeds this value it begins to act as an SNRI as well. The side effect of greatest concern with this particular drug is dose related increase in diastolic blood pressure.

In 2004, Devanand et al. published a study on treatment response and side effects of extended release venlafaxine (Effexor ER) among older adult outpatients with dysthymic disorder. Twenty-three participants ≥60 years old were enrolled in this open-label trial (Devanand et al., 2004). Criteria for response were as follows: ≥50% reduction in 24-item HAM-D score and a CGI severity score of 1 or 2. Approximately 78% of those who completed the study were responders. Remission, on the other hand, required a final 24-item HAM-D score of ≤6. Approximately half (47.8%) of the sample met criteria for remission. Factors associated

with superior treatment response included increased severity of depression at baseline, while comorbid cardiovascular disease was associated with poorer treatment response. In this particular study, the mean venlafaxine dose was 174 mg/day with a range of 150 mg/day to 300 mg/day. Before the 12-week treatment period was completed, 5 individuals dropped out of the study—3 due to side effects and 2 for personal reasons. Overall, however, venlafaxine was well-tolerated, and no significant changes in systolic or diastolic blood pressure were noted. Tolerability may have been enhanced by use of the extended release formulation of venlafaxine.

Limitations of this study include lack of a control group and small number of participants. Eighty percent of participants were self-referred. This group of individuals may be more or less likely to respond to antidepressant therapy thus limiting the applications of the study. In addition, 87.5% of participants where white and approximately 70% were male. Furthermore, this study did not include individuals with cognitive impairment or dementia. One's ability to extrapolate data from this study is, therefore, limited by the small and fairly homogenous population sampled.

Other drugs that have emerged as potential treatments for dysthymia include dopaminergic drugs which increase neurotransmission in the mesolimbic system and acetyl-L-carnitine (Bellino et al., 2000). Mesolimbic dopamine mediates rewarding, motivating, and incentive effects of various stimuli. Symptoms of dysthymia such as lack of interest, lack of motivation, and lack of concentration have been attributed to deficiencies of this particular neurotransmitter. Unfortunately, there are no studies regarding dopaminergic drugs exclusively among adults over the age of 60. Acetyl-L-carnitine is yet another drug that has shown potential in the treatment of depressive conditions such as dysthymia. This drug was initially indicated for the treatment of cerebral involutive pathologies such as melancholia (Bella, Biondi, Raffaele, &

Pennisi, 1990). Both the chemical structure and spatial conformation of acetyl-L-carnitine mimic these same features of acetylcholine. Administration of this drug has, therefore, been noted to induce behavioral changes associated with stimulation of cholinergic pathways. Of particular interest to the study of dysthymic disorder is evidence suggesting that acetyl-L-carnitine mediates serotoninergic neurons as well.

Efficacy and potential side effects of acetyl-L-carnitine have been tested in a randomized controlled trial in older adults with dysthymia (Bella et al., 1990). Sixty total participants, all between the ages of 60 and 80, were randomly assigned to 1 of 2 groups following a 1 week washout period. Participants in the treatment group received 1.5 g acetyl-L-carnitine twice daily, while those in the control group received a placebo twice a day. Participant scores on the Hamilton Rating Scale for Depression (HAM-D), Beck Depression Inventory (BDI), and Sandoz Clinical Assessment-Geriatrics (SCAG) were compared at baseline and 60 days following initiation of treatment or placebo. Statistical analysis of these scores indicated that acetyl-L-carnitine induced a significant reduction in severity of depressive symptoms. Information regarding adverse effects and tolerability is more limited. Four participants in the treatment group and 10 participants in the control group did not complete the study. No information is provided as to why these individuals dropped out. The authors concluded that acetyl-L-carnitine was well-tolerated, but provided no detailed information.

Pharmacotherapy Across Adult Age Groups

Across all adult age groups, drug therapy has been shown to reduce, and in some cases eliminate, depressive symptoms associated with dysthymic disorder. In their review of 25 randomized, controlled trials evaluating pharmacotherapy of dysthymia, De Lima and Hotopf (2003) calculated the relative risk for treatment response to be 0.68 for TCAs, 0.68 for SSRIs,

and 0.59 for MAOIs. The number needed to treat (NNT), or the number of individuals that must be treated in order to have one successful outcome, was also determined. The NNT for TCAs, SSRIs, and MAOIs was 4.3, 5.1, and 2.9 respectively. Based on these findings, De Lima and Hotopf concluded that newer antidepressants such as the SSRIs are just as effective in the treatment of dysthymia as TCAs and MAOIs. TCAs, though, were shown to produce significantly more side effects than placebo and the other drug classes such as SSRIs. Because SSRIs tend to be more expensive, however, both side effect profile and cost must be considered in the initiation of drug therapy in individuals with dysthymia.

In their review of drugs versus placebo for dysthymia in the general adult population, Lima et al. (2003) also concluded that pharmacotherapy was an effective method for treating dysthymia and that TCAs, MAOIs, and SSRIs were equally effective. In addition, they reviewed the side effect profile for each class of drugs. Individuals treated with a TCA had higher rates of constipation, dizziness, dry mouth, and deficits in visual accommodation than the other drug classes. SSRIs were associated with sweating, nausea, sexual dysfunction, insomnia, and dry mouth. The side effect profile for MAOIs could not be reliably obtained because only 1 study of an MAOI was included in this review. Lima et al recommended that the side effects for each class be considered in the context of patient preferences and comorbidities when initiating drug therapy for dysthymia.

In 2005, Lima et al added to this body of knowledge in their review of randomized, controlled trials performing a direct comparison of various antidepressants and their effect on DD. In a single study comparing the SSRI sertraline (50-100 mg/day) and the TCA imipramine (50-100 mg/day), there was no significant difference in treatment response or remission rates among adult patients with dysthymia. There were, however, more dropouts due to side effects in

the imipramine group. A meta-analysis of three studies comparing the TCA imipramine to either penelzine or moclobemide (both MAOIs) was also performed. Although there was no statistically significant difference in the efficacy of imipramine and the MAOIs, moclobemide did achieve higher remission rates. There were no differences in dropout rates between the TCA and MAOIs.

Special Pharmacological Issues in Older Adults

While these studies regarding pharmacologic agents and their effect on dysthymia in the general population are useful, reported findings must be applied to older adults with caution. Understanding pharmacology and medication adherence among the elderly is essential for providing these individuals with effective psychiatric pharmacotherapy. Absorption, distribution, metabolism, and excretion of medication vary with age (Cavanaugh & Blanchard-Fields, 2006). Absorption slows down as the transit time between the stomach and small intestine increases. Distribution also changes with age as total body water decreases, and total fat increases. In addition, more drug remains free in the blood rather than bound to plasma proteins. These changes in distribution mean that as one ages, various drugs can build up to toxic levels more rapidly. Decreases in the rate of drug metabolism and excretion, as a result of decreased hepatic and renal function, are also responsible for increased adverse effects and drug toxicity among older adults.

The dangers of drug therapy can be minimized if the strategy of "start low and go slow" is employed throughout the initiation of medication within this patient population (Cavanaugh & Blanchard-Fields, 2006). Some physicians recommend using one third to one half of the usual adult dosage when prescribing a drug with a narrow therapeutic window. In general, drug choices among older adults should have minimal antihistaminic, anticholinergic, and

antiadgrenergic effects; minimal cardiovascular risk; and minimal drug-drug interactions (Zisook & Downs, 1998). Although such consideration should be made when selecting drugs in any age group, changes in drug absorption, distribution, metabolism, and excretion, as well as an increase in number of medications taken make individuals of advanced age more vulnerable to these adverse effects.

Drug adherence itself becomes a problem in geriatric medicine due to polypharmacy (Cavanaugh & Blanchard-Fields, 2006). Drug regimens become very complicated as the number of one's medications increases. Some drugs must be taken on an empty stomach, while others must be taken after a meal. There are also medications that are taken on a regular schedule and others that are taken as needed. Of those drugs taken on a regular schedule, some are taken three times a day and others are taken once or twice a day. In addition to polypharmacy, sensory changes such as decreased vision and hearing, physical limitations such as arthritis and weakness, and cognitive changes including dementia can negatively impact medication adherence among older adults (Cavanaugh & Blanchard-Fields, 2006). Adherence to medication regimens can be improved by minimizing the number of drugs prescribed for each individual patient. If, however, each drug is essential, periodic checks should be made to access the need for each drug as well as the patient's adherence (Cavanaugh & Blanchard-Fields, 2006). Prescribing needed drugs with the simplest dosing regimen may also contribute to increased compliance.

Psychotherapy

Psychotherapy, an interpersonal intervention, provides individuals with the tools required to comprehend and master problems associated with depressive conditions such as dysthymia. After the completion of therapy, these tools continue providing individuals with a sense of control that allows them to self-manage their symptoms of depression (Paykel, 1995). There are many forms of psychotherapy, but two forms, cognitive behavioral and interpersonal psychotherapy, have been found to be particularly effective in treating elderly patients with major depressive disorder (Bellino et al., 2000). While these forms of psychotherapy have not been evaluated exclusively in adults over the age of 60 with pure dysthymia, they have been studied in a more general adult population with this disorder.

Psychotherapy Across Adult Age Groups

Cognitive behavioral psychotherapy (CBT) comes in many forms but all are time-limited and structured in their approach to the treatment of dysthymia. CBT focuses on the negative cognitions that perpetuate chronic depression (Markowitz, 1996). Throughout face-to-face sessions with a therapist and completion of homework assignments, the individual with dysthymia begins to restructure their characteristic way of viewing and interacting with the world (Markowitz, 1996; McCullough, 1984). In 1991, an article was published regarding a study of six dysthymic patients of unspecified age and their response to fifteen, hour-long CBT sessions. Prior to initiation of the study, all participants gradually discontinued their use of antidepressants or anxiolytics (Stravynski, 1991). Measures used to assess treatment response included the Beck Depression Inventory (BDI), the Hamilton Rating Scale for Depression (HAM-D), the Hopelessness scale, and the Automatic thoughts questionnaire. The Hopelessness Scale is a 20- item self-rating questionnaire that assesses pessimism and suicidal tendencies,

while the Automatic thoughts questionnaire is a self-rated measure of dysfunctional thoughts. At study completion, significant improvement in depression and reduction in irrational thinking were observed among these individuals with dysthymia. Five study participants showed clinically significant improvement, and 4 out of 6 participants no longer met criteria for dysthymic disorder at 6 month follow-up. Although this study was uncontrolled and contained a small number of participants, it suggests that CBT does improve mood in a select number of individuals with dysthymic disorder. Larger, controlled studies will be needed to assess how these results apply to a more diverse population.

One form of CBT, Cognitive-Behavioral Analysis System of Psychotherapy (C-BASP), has been specifically developed for use in patients with chronic forms of depression including dysthymia (McCullough, 2003). C-BASP focuses on both interpersonal and intrapersonal conflicts that contribute to the development of DD (McCullough, 1984). C-BASP requires the patient to analyze problematic events in sequential order (McCullough, 2003). Each session of C-BASP explores a single event. The patient is asked about the personal meaning he or she attributes to the given event. In doing so, the therapist elicits the patient's emotional responses to the situation and helps the client understand that many mood reactions are possible (McCullough, 1984). Once individuals recognize the number of mood reactions possible, they begin to recognize the role they play in creating and maintaining their present mood (McCullough, 2003). The therapist then initiates a discussion regarding the patient's behavioral responses to the event and how these responses affected the outcome. The client's ability to connect behavior with consequences is essential for achieving an end to chronic depression (McCullough, 2003). Finally, the clinician assists the client in proposing alternative thoughts and behaviors that may have resulted in a more positive outcome.

The effect of C-BASP on a group of 10 individuals of unspecified age with dysthymic disorder was evaluated by J.P. McCullough (1991). The mean number of therapy sessions completed by participants was 31, with a range of 14 to 44 sessions. The duration of therapy was, on average, eight months representing once-per-week therapy sessions. The two outcome measures used to analyze the efficacy of C-BASP were the Beck Depression Inventory and the Rotter Locus of Control Scale. The Rotter Locus of Control Scale assesses the level of control individuals feel they possess in regards to their emotions and life experiences. A score of ≤10 indicates an internal locus of control, or the feeling that one possesses the ability to direct their own view of the world. Using these two outcome measures, 9 of 10 participants were found to be in remission at study completion. The 9 remitters, with the exception of one individual who was only available for follow up at 16 months, were also in remission for 2 or more years following study completion.

Unfortunately, the authors fail to clarify if any patients were being treated with anti-depressants throughout the course of the study. Additional limitations include small sample size and poor generalizability. Generalizability is limited by the sample which consisted of only self-referred white individuals of middle-socioeconomic status. In addition, 4 of the original 20 participants did not complete the study and no explanation for their leaving is provided by the authors.

Interpersonal psychotherapy (IPT) is another psychotherapeutic approach that has been studied in the treatment of dysthymic disorder and other depressive conditions. Like CBT, IPT is time-limited and manualized (Markowitz, 1996). Throughout the process of IPT, patients begin to develop interpersonal skills enabling them to effectively cope with interpersonal conflict. Standard IPT focuses on a recent adverse life event which involves one of four problem

areas: grief, role dispute, role transition, or interpersonal deficits (Markowitz, 1996). Because IPT was initially developed for the treatment of an acute, depressive episode, adaptations have been made to allow its use in chronically depressed individuals. In interpersonal therapy adapted for use in dysthymia (IPT-D), an iatrogenic role transition is created as the focal point of treatment (Markowitz, 2003). This iatrogenic role transition describes the process by which patients with DD alter their perception of interpersonal deficits which they previously attributed to a character flaw and eventually come to contribute to their illness. A study comparing the efficacy of interpersonal psychotherapy for dysthymia (IPT-D), brief supportive psychotherapy (BSP), sertraline, and sertraline plus IPT-D will follow in the section on combined therapy.

Special Psychotheraputic Issues in Older Adults

When recommending psychotherapy to older adults, one must be particularly sensitive to the stigma associated with mental health conditions among this patient population (Unutzer et al., 1999). This stigma may be overcome by explaining the biological basis for dysthymia and providing the individual with other information regarding his or her condition. If older adults are entirely resistant to psychotherapy, other non-conventional psychosocial interventions may be employed (Zisook & Downs, 1998). These interventions include the use of pet therapy and touch for individuals without regular social contacts.

Other barriers to psychotheraputic intervention for dysthymia in older adults include transportation and cost (Pinquart et al. 2006). Transportation is of concern due to the number of older adults who are unable to drive. Co-morbid medical conditions as well as other changes associated with aging such as decreased visual acuity, difficulty maintaining and shifting attention, and decreased reaction time can make driving unsafe in this patient population (McKnight, 2003). While the cost of psychotherapy may be a concern in all patient cohorts,

older adults may be particularly unable to afford this form of treatment as a result of a fixed income or no income at all. While Medicare Part B covers 80% of most outpatient healthcare services including doctors visits for antidepressant medication monitoring and adjustment, it only covers 50% of psychotherapy expenses (Department of Health and Human Services, 2007).

Pharmacotherapy versus Psychotherapy

Trials demonstrating the efficacy of pharmacotherapy versus psychotherapy are also beneficial in evaluating these therapeutic options. Two studies referred to collectively as the Treatment Effectiveness Project provide a head-to-head comparison of the SSRI paroxetine (Paxil) and problem solving treatment-primary care (PST-PC) (Barrett et al., 2001; Williams et al., 2000). One study assesses paroxetine and PST-PC in patients with dysthymia and minor depression between 18 and 59 years of age, and the other evaluates these therapeutic options in older adults ≥ 60 years of age.

Problem solving therapy-primary care (PST-PC) is another CBT approach using brief psychotherapy to treat depressive conditions including dysthymia. PST-PC, designed specifically for use in the primary care setting, is based in part, on behavioral therapy principles (Barrett et al., 1999). PST-PC also focuses on the association between one's mood and problems encountered by this individual. Establishing this association in the mind of the patient requires three steps: 1.) the patient must recognize how their mood can be related to their problems, 2.) problems are explicitly defined and characterized by the patient, and 3.) the patient must attempt to solve these problems in an ordered fashion (Barrett et al., 1999). Problem solving treatment in the primary care sector typically involves 4-6 sessions that are approximately 30 minutes in duration.

The designs of the paired studies referred to above were identical. Participants were divided into three groups: placebo, paroxetine, and PST-PC. Treatment duration, regardless of group, was 11 weeks. Participants in the PST-PC group received 6 PST-PC sessions over this 11 week period. Paroxetine was initiated at 10 mg/day. This dose was increased at week 2 to the target dose of 20 mg/day, a dose that could be increased to a maximum of 40 mg/day if partial or

no improvement were achieved later in the study. A follow-up assessment was also included at 25 weeks post-treatment initiation. The primary outcome measure at study completion and follow-up was the 20-item Hopkin's Symptom Checklist (HSCL-D-20), a self-report of depression, anxiety, interpersonal sensitivity, hostility, and somatization (Barrett et al., 1999).

Pharmacotherapy versus Psychotherapy in Older Adults

In the study of older adult patients ≥ to 60 years old, all participants in each group (placebo, paroxetine, and PST-PC) exhibited improvement in HSCL-D-20 scores at study completion (Williams et al., 2000). Intent-to-treat analysis of the entire sample indicated an advantage for paroxetine over placebo regarding symptomatic improvement, but no such advantage was observed for PST-PC. Those participants in the PST-PC group did, however, exhibit more rapid symptom resolution than was observed in the placebo group. Remission rates, or the percent of individuals with a HAM-D score of <7, were also determined and found to be relatively high. Among patients with DD, 45.6 % of those receiving paroxetine, 50.8% of those receiving PST-PC, and 40.3% of those receiving placebo were defined as remitters at study completion. The differences between remission rates were not statistically significance. This study differs from other studies on dysthymia in the elderly in that it included a more equal distribution of men and women and a larger proportion of minorities. Furthermore, the average patient in this study reported 3.4 chronic medical conditions. These study characteristics allow the results of this study to be more reasonably applied to a greater number of older adults.

Pharmacotherapy versus Psychotherapy Across Adult Age Groups

In the study comparing paroxetine, PST-PC, and placebo in patients between 18 and 59 years of age, a total of 241 individuals were randomly divided into the three groups (Barrett et al., 2001). The HSCL-D-20 scores for all three groups significantly declined over the 11-week

period, but did not differ significantly in relation to one another. Individuals in the paroxetine and placebo groups exhibited more rapid symptom resolution throughout the first two weeks of treatment. This rate of symptom resolution, however, slowed down in subsequent weeks during which response to PST-PC became more rapid. The remission criterion in this study was a HAM-D score of ≤6. Remission rates were significantly higher for paroxetine and PST-PC than for placebo: 80% percent for those treated with paroxetine, 56.8% of those treated with PST-PC, and 44.4% for those treated with placebo.

The two studies described above allow for direct comparison of treatment efficacy seen in young to middle age adults with DD to treatment efficacy in adults over the age of 60 with DD. While paroxetine proved superior to PST-PC and placebo in symptom resolution among adults 60 and older, it was not significantly superior to either group in regards to remission rates. In adults 18 to 59, paroxetine, PST-PC, and placebo did not differ significantly in symptom resolution, but paroxetine and PST-PC were superior to placebo in achieving remission.

One additional study providing a comparison of pharmacotherapy and psychotherapy across adult age groups was located. This study compared cognitive therapy to the SSRI fluoxetine and included a group of patients with DD between the ages of 18 and 60. These patients were randomly assigned to receive either 20 mg/day of fluoxetine (a dose that was not adjusted throughout the course of the study) or weekly cognitive therapy (Dunner et al., 1996). A total of 24 patients were assessed at week 8 and 22 patients at week 16. Based on the Beck Depression Inventory (BDI) and the Hamilton Depression Rating Scale (HAM-D), significant within group differences were noted from baseline to both weeks 8 and 22 for patients treated with fluoxetine and patients treated with CBT (Dunner et al., 1996). Significant between group differences were not noted, however. Remission criteria were as follows: HAM-D ≤7 and BDI≤

to 8. According to these criteria, 7 fluoxetine patients and 2 cognitive therapy patients were labeled as remitters at week 16—not a significant difference (Dunner et al., 1996). Individuals with serious concomitant medical illness were excluded from this study which makes application of these results to older adults problematic.

Combination Therapy

In general, experts in the field of mood disorders recommend combination therapy, pharmacotherapy combined with psychotherapy, to treat chronic forms of depression (Arnow & Constantino, 2003). While randomized, controlled trials do exist regarding combination therapy in a general population of individuals with dysthymia, there are no such trials performed exclusively among older adults with DD.

Combination Therapy Across Adult Age Groups

In 1999, Ravindran et al. studied the effects of the SSRI sertraline versus sertraline plus group cognitive behavior therapy (GCBT) among 97 patients between the ages of 21 and 54 with dysthymia. GCBT provides individuals with dysthymic disorder, who typically suffer from social isolation and poor interpersonal skills, with an opportunity to improve their interactions with and behaviors towards others. The Hamilton Rating Scale for Depression (HAM-D) was used to assess patient symptoms throughout the study. Forty-seven study participants received sertraline (mean maximal dose of 177.90 mg/day), and 50 participants received placebo (Ravindran et al., 1999). Of the 47 subjects receiving sertraline, 25 received group cognitive behavioral therapy as well. The GCBT consisted of groups of 7-10 participants who met for 12 weekly therapy sessions. During these group meetings, emphasis was placed on dysfunctional thought processes and automatic negative thoughts. Treatment response was defined as a score of < 10 on the HAM-D scale and at least a 50% reduction in this score from baseline (Ravindran et al., 1999). After 12 weeks, combination therapy achieved a greater percentage of responders than did the sertraline only group; however, this difference did not achieve statistical significance. Quality of life measures, including health perception, energy/vitality, cognitive functioning, alertness, social interaction, and life satisfaction, among patients in the sertraline-

only group improved to levels beyond those noted in the placebo group (Ravindran et al., 1999). These same measures did not appear to vary as a function of combination therapy.

The small number of study participants may have prevented the marginal advantage seen in the combination therapy group from reaching statistical significance. Furthermore, the 12 week duration of GCBT may not have been long enough to achieve maximal benefits in this group of chronically depressed individuals. Unfortunately, this study excluded participants with any physical illness which makes extrapolation to the geriatric population especially difficult.

In another study, interpersonal psychotherapy for dysthymia (IPT-D), brief supportive psychotherapy (BSP), sertraline, and sertraline plus IPT-D were compared in a group of 94 subjects (ages 18-60) with pure dysthymia over a 16 week period (Markowitz, Kocsis, Bleiberg, Christos, & Sacks, 2005). Brief supportive psychotherapy, an active but less specific treatment, served as the control group treatment in this particular study. Those individuals receiving IPT-D, BSP, and combination IPT-D and sertraline, attended on average 13.2, 9.6, and 12.8 sessions respectively. These sessions were 45-60 minutes the first week and 20-30 minutes during subsequent weeks. Study participants receiving sertraline therapy began taking 50 mg/day—a dosage that was increased by 50 mg/day until the participant reached a dose of 200 mg/day or adverse effects were noted. The primary outcome measure for this study was the final 24-item HAM-D score, with response defined as a greater than 50% reduction in mean HAM-D score. Response rates among the four groups were as follows: 58.3% for sertraline, 57.1% for combined treatment, 34.8% for IPT-D, and 31.0% for BSP. Remission was defined as a final HAM-D score <7 and Global Assessment of Functioning score >70. A Global Assessment of Functioning score of >70 indicates no more than slight impairment in social and occupational functioning. Forty-two percent of individuals treated with sertraline, 52% treated with

combination therapy, 22% treated with IPT-D, and 12% of those treated BSP achieved remission (Markowitz et al., 2005). Overall, this study yielded no statistically significant differences between sertraline with IPT-D and sertraline alone which the researchers state might be explained by insufficient power to detect such a difference.

Cognitive Interpersonal Group Psychotherapy for Chronic Disease (CIGP-CD) is another form of psychotherapy which was studied in combination with the SSRI fluoxetine (Hellerstein et al., 2001). This particular form of psychotherapy combines cognitive and interpersonal approaches to chronic depression. Following an 8 week trial of fluoxetine, individuals achieving a ≥40% decrease in Hamilton Rating Scale for Depression (HAM-D) score and a Clinical Global Impression (CGI) score of 1 or 2 were identified (Hellerstein et al., 2001). These study participants, ages 21-65, were then randomly divided into two additional groups. One group continued to receive fluoxetine only, while the other received fluoxetine in combination with CIGP-CD. During group sessions, patients were educated regarding dysthymia and were also encouraged to practice open communication with one another. Group members were asked to assist other members of the group in their transition from a pessimistic outlook on life to one that was more hopeful. Treatment duration for all study participants was approximately 24 weeks following the initial dose of fluoxetine (Hellerstein et al., 2001). Response criteria following the second phase of this study were a 50% decrease in HAM-D score over the 24 week period and a final score of 1 or 2 on the CGI scale. Based on these criteria, 89% of combined treatment subjects were responders, while 76% of medication-only patients responded to therapy (Hellerstein et al., 2001). At follow-up, 61% of combination subjects and 40% of medication-only subjects were labeled as responders. The differences in response rates at study termination and follow-up were non-significant. Remission rates (defined as HAM-D item #1 score of 0 and

no longer meeting DSM-IV criteria for dysthymia) were also higher, yet non-significantly, at study completion and follow-up in the combination group vs. the fluoxetine-only group.

Conclusion

As the number of adults over the age of 60 continues to grow, healthcare providers must be prepared to meet the needs of this unique patient population. Mental disorders are a concern not only in their own right, but also due to the role they play in physical disease and overall level of functioning. As such, particular attention must be paid to this realm of health. While major depressive disorder research at all stages of life is well-represented in the literature, research regarding dysthymic disorder is not—especially among older adults. In order to obtain an understanding of effective treatment options for this population, it is important to summarize what it is we know and where research and clinical attention need to be focused in the future.

First, this review confirms what others have already found—that there is a paucity of research on depression treatment in the elderly. There have been three recent reviews comparing pharmacotherapy and psychotherapy for depression (broadly defined) in the older adult, where only two (Klawansky, 1997), four (Gerson, Belin, Kaufman, Mintz, & Jarvick, 1999), and thirty-two studies (Pinquart, Duberstein, Lyness, 2006) were identified that examined psychotherapy in this population. The studies identified were examining major depression, double depression, and dysthymia. Two of the above mentioned reviews suggest no difference in efficacy between pharmacotherapy and psychotherapy with pharmacotherapy having a slight advantage, while one suggests that psychotherapy for dysthymia alone appears to do better than pharmacotherapy in older adults.

In the 5 studies discussed in this review examining psychotropic medication use specifically for dysthymia in older adults, fluoxetine, sertraline, venlafaxine, and acetyl-L-carnitine all demonstrated an ability to reduce dysthymic symptoms. Given the small number of studies (5), their limitations (some without control groups, patient recruitment, gender and

cultural issues), and the very small number of participants (N=246 across studies), this is all we are able to conclude. Well-controlled studies recruiting older adults only with dysthymia will be needed to best determine the appropriate treatment for this patient population.

The only other study that specifically addressed dysthymia in older adults compared the efficacy of paroxetine and PST-PC. In this particular study, patients taking paroxetine achieved greater symptomatic response than did those patients undergoing PST-PC. Unfortunately, no other research exists in older adults to suggest that drug therapy is superior, inferior, or comparable to other forms of psychotherapy such as CBT and interpersonal psychotherapy. Theoretically CBT and interpersonal psychotherapy should be especially useful among older adults whose onset of dysthymia is typically preceded by inter- and intrapersonal conflicts. These conflicts include role transitions that occur with aging, loss of family members or friends, and the diagnosis of chronic medical conditions. Until we have a number of randomized, controlled clinical trials testing these therapies, however, we will be unable to adequately access their effectiveness among older adults. The results of trials such as these may be particularly important for older adults who are unable to tolerate the side effects of SSRIs or who are unable to take them because of drug interactions or medical co-morbidities.

Based on the evidence presented here, SSRIs should be considered first line therapy for adults 60 or older suffering from dysthymic disorder because they have been proven safe and modestly effective in this patient population. It remains an empirical question as to whether any individual SSRI or SNRI might be most effective among older adults. If an older adult is not achieving adequate symptom resolution with an SSRI alone, combination therapy should be considered, as anecdotal evidence (Arnow & Constantino, 2003) does indicate that such therapy may maximize therapeutic response. Although there are not an adequate number of studies to

suggest that psychotherapy should be used first line for dysthymic disorder in adults over the age of 60, this form of treatment should be used in all patients unable to tolerate or take SSRIs or who have had success with psychotherapy in the past.

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Abstract

Objective: This scholarly project is a qualitative review of treatment options available for dysthymic disorder (DD) in older adults.

Method: This is a qualitative review based on articles collected from a search of MEDLINE, CINAHL, PubMed, PsycINFO, Cochran Review, and Science Citation Index databases. Key words used for this search included "dysthymic disorder," "treatment of dysthymic disorder," "and "dysthymic disorder in late life."

Results: Five studies regarding pharmacotherapy and one study regarding pharmacotherapy versus psychotherapy found SSRI's to be effective in treating dysthymia in the elderly. No conclusions were reached regarding psychotherapy for this population as there were an insufficient number of studies to review.

Conclusion: SSRIs should be considered first line therapy for adults ≥60 years old with DD. If an older adult is unable to achieve adequate symptom resolution with an SSRI alone, combination therapy should be considered. A psychotherapeutic approach should be used in all patients unable to tolerate or take SSRIs.