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Article 65

Candidates for Antidepressants: Assessing a History of Early Life Stressors

Dixie Meyer

Meyer, Dixie, D., is an assistant professor in the Medical Family Therapy Program in the Department of Family and Community Medicine at Saint Louis University. Her research interest areas include neurobiological applications in counseling, attachment, early life stressors, and couples counseling.

Abstract

Depression may be a debilitating condition. Many individuals turn to antidepressants to treat their symptoms. Research suggests that while many individuals report success and symptom reduction with antidepressant usage, a large portion of individuals with depression do not respond to antidepressant treatment. The etiology of depression for many individuals may be attributed to early life stress (ELS). ELS may lead to a malfunctioning stress response system. For example, stress hormone levels may be elevated in those individuals with a history of ELS. Most antidepressants are designed to affect the neurotransmitters serotonin, norepinephrine, and or dopamine and not stress hormones. For those individuals who are nonresponsive to antidepressant treatment, they may need a medication that alters stress hormones. When counseling clients using antidepressants, counselors should be prepared to serve as a medication manager and liaison between the client and antidepressant prescribing physician.

Antidepressants were discovered when individuals given medications to treat tuberculosis demonstrated an improved mood (Ingersoll & Rak, 2006). At this advent, the thought of medically treating depression, a psychological disorder, was revolutionary. This particular form of antidepressants, mono amino oxidase inhibitors (MAOIs), hinders enzymes that break down serotonin, norepinephrine, and dopamine (Stahl, 2008). The discovery of MAOIs led to a different understanding of depression. It demonstrated that depression could be treated by altering neurochemical function. However, without careful restriction of the diet, MAOIs produce dangerous side effects (Stahl, 2008). Tricyclic antidepressants (TCAs) were also discovered early on. However, the effects on multiple systems, including serotonin and norepinephrine pre-synaptically and acetylcholine, norepinephrine, and histamine post-synaptically, lead to an increase in potential side effects (Stahl, 2008).

The development of selective serotonin reuptake inhibitors (SSRIs) led to a new era of antidepressants. The selectively altering of one system appeared safer than other antidepressants that affected multiple systems (Ingersoll & Rak, 2006). Since the 1980s, when SSRIs emerged, prescriptions for antidepressants have risen exponentially. It is

estimated that 11% of adults are currently taking an antidepressant (CDC, 2011). Other forms of antidepressants have also been developed. In recent years, serotonin norepinephrine reuptake inhibitors (SNRIs) and atypical antidepressants like bupropion (a norepinephrine and dopamine reuptake inhibitor; NDRI) and serotonin antagonist reuptake inhibitors (SARI) have also been highly prescribed (Stahl, 2008). While many antidepressants are prescribed in isolation to treat depression, multiple medications may be prescribed. For example, bupropion may be written as an adjunct to a SSRI (Stahl, 2008).

The many forms of antidepressants are currently among the most commonly prescribed medications in the United States (National Center for Health Statistics, 2011). In fact, between 1996-2007 prescriptions for antidepressants written by primary care physicians, with limited training in mental health disorders, more than doubled (Mojtabai & Olfson, 2011). Factors like etiology and duration of depression determine the course of treatment for depression. Yet, these are factors many primary care physicians do not have the educational background to confidently deduce. Mental health professionals often counsel clients on a weekly basis; therefore, mental health professionals are in a critical position to help clients with medication management. It is imperative that mental health professionals are knowledgeable about who are the best candidates for antidepressants. This information may help mental health professionals collaborate with physicians in the treatment of individuals presenting with depression.

Effectiveness of Antidepressants

Research suggests that antidepressants may not be as effective as hoped. Greenberg and Fisher (1997) reported results from a meta-analysis of clinical trials and suggested SSRIs had a slight superiority over placebo. The authors argued, however, that this could have been attributed to research methodology, not actual differences. While this meta-analysis had favorable results, others did not. Two additional meta-analyses of clinical trials of SSRIs failed to find that SSRIs outperformed placebo (Kirsch & Sapirstein, 1998; Moncrieff & Kirsch, 2005). It should be noted, however, that the placebo effect is efficacious. Failure to exceed placebo does not indicate that success was not present. In fact, Ross (1995) attributed 30% of treatment response to the placebo effect.

Including other newer antidepressants in a review of the efficacy of the medication is not more promising. Kirsch et al. (2008) conducted a meta-analysis of all the clinical trials (n=47) of antidepressants conducted from 1987 through 1999. Medications included fluoxetine (SSRI), citalopram (SSRI), venlafaxine (SNRI), nefazodone (SARI), sertraline (SSRI), and paroxetine (SSRI). The effectiveness of these medications was below the recommended standard of clinical significance. However, clinical significance was reached with severely depressed participants. This was attributed to a decrease in placebo efficacy and not an increase in antidepressant efficacy. Based on the lack of clinical support for many antidepressants, it is important to determine what symptoms may persist with antidepressant treatment. McClintock et al. (2011) utilized data from a large scale study (Sequenced Treatment Alternatives to Relieve Depression, STAR*D) to analyze what depressive symptoms were residual after antidepressant treatment for individuals not reaching remission. Results suggested

sadness, difficulty concentrating and making decisions, and sleep difficulties were the most pervasive.

The Role of Cortisol in Depression

As previously noted, the majority of antidepressants increase serotonin, norepinephrine, and or dopamine levels. With concerns raised over the effectiveness of antidepressants, perhaps a look at the neurobiology behind depression should be assessed. While many individuals report success with their antidepressant and research suggests that serotonin, norepinephrine, and dopamine may underlie depression (Julien, Advokat, & Comaty, 2011; Stahl, 2008), other neurochemicals may be involved.

The hypothalamic-pituitary-adrenal (HPA) axis is a biological system known to regulate stress reactivity (Heim, Plotsky, & Nemeroff, 2004). The stress response begins in the brain where the neurochemical precursor corticotropin-releasing factor (CRF), released from the hypothalamus, stimulates adrenocorticotropic hormone (ACTH), released from the pituitary gland (Heim et al., 2004). The release of CRF and ACTH results in the release of cortisol from the adrenal gland (Heim et al., 2004). Cortisol is a stress hormone. Cortisol and its precursors are consistently implicated in depression (Dinan, 1994; Nemeroff & Vale, 2005; Nestler et al., 2002; Pariante & Lightman, 2008; Pariante & Miller, 2001; Tofoli, Baes, Martins, & Juruena, 2011).

Overall, individuals with depression often have elevated cortisol levels and express an exaggerated cortisol response following the release of cortisol precursors (e.g., CRF, ACTH; Pariante & Miller, 2001). This may suggest overactivity of the HPA axis, thus leading to overproduction of the cortisol. Individuals may also be resistant to cortisol (Gunnar & Vazquez, 2001). This suggests that the individual is inoculated to the stress hormones released in response to stressors. Resistance to cortisol may be indicative of reduced biological responsiveness to stressors. In other words, the range of cortisol output is more limited in response to a stressor with individuals who are resistant to cortisol. Many individuals with depression also have flattened diurnal profiles (Gunnar & Vazquez, 2001). The flattened profiles are indicative of lower than the average individual's cortisol levels upon awakening, and yet cortisol levels remain higher throughout the course of the day. This yields higher daily cortisol output.

Cortisol and Early Life Stressor Trauma

While the research is convincing related to cortisol and depression, there is also research to the contrary (Peeters, Nicolson, & Berkhof, 2004; Strickland, Deakin, Percival, Dixon, Gater, & Goldberg, 2002). Specifically, Peeters et al. (2004) found no relationship between elevated cortisol levels and depression. It may be a specific subset of individuals with depression that exhibit elevated cortisol levels and that not all individuals with depression have altered HPA axis activity (Strickland et al., 2002). The etiology of depression needs to be considered. The conflicting research related to cortisol levels in individuals with depression may be contributed to adverse events. For many individuals, depression is attributed to a stressor in childhood (early life stress, ELS). Tofoli and colleagues (2011), based on their results from a meta-analysis examining the relationship between ELS and depression, suggested that individuals with a history of ELS may be at an increased risk for developing depression. Neurochemical alterations

associated with a history of ELS may be to blame. These individuals may have a malfunctioning HPA system due to the environmental influences occurring in childhood. Research reliably reports an association between increased cortisol levels and childhood traumas or ELS. For example, Pariante and Lightman (2008) suggested that malfunctioning in the cortisol regulating system may be related to early life stressors. They further noted that the malfunctioning HPA axis makes an individual vulnerable to developing depression later in life.

The etiology of increased activity of the HPA axis leading to elevated levels of cortisol may begin as early as infancy. Murgatroyd et al. (2009) examined the neurobiological underpinnings of infant mice separated from their mothers. The authors noted that the separated mice were more likely to have increased activity in the HPA axis than the mice reared with their mothers. Similar results are also noted with humans (Luijk et al., 2010). The equivalency of stress produced by maternity separation in mice may be the type of bond formed between infants and their primary caregiver (typically their mothers). The bond between the infant and mother may be defined through the quality of the attachment formed. One type of attachment may be a secure attachment where the infant trusts that his or her mother will be available to him or her when needed (Ainsworth, Blehar, Waters, & Wall, 1978). With insecure attachments, the bond between the infant and mother is not dependable (Ainsworth et al., 1978). Examples of insecure attachments may be attributed to the infant avoiding the primary caregiver more frequently, known as the insecure-avoidant type, or the infant may display more anxious behaviors around the primary caregiver, known as the insecure-resistant type. Another type of insecure attachment is the disorganized attachment, and it may be formed when the infant experiences some trauma in the relationship with his or her primary caregiver (Main & Cassidy, 1988). Luijk et al. (2010), in their study of attachment style, maternal depression, and cortisol responses, reported that infants with an insecure-resistant attachment style had higher cortisol responses pre- and post-psychosocial stressor experience. Furthermore, those infants with a disorganized attachment style had a more flattened diurnal pattern of cortisol.

The findings related to disruptions in the attachment process may be of particular relevance for counselors. Counselors may want to examine attachments to primary caregivers when clients have difficulty in relationships. The difficulties may present as clients with children who are having difficulty connecting with their children or in family counseling when children are afraid of one or both parents. Furthermore, adult clients may also display insecure attachment behaviors in romantic relationships. Clients presenting with constant worry about their romantic partners' faithfulness or who report difficulty feeling close to romantic partners may be demonstrating disruptions in bonding with their primary caregivers. As suggested in the research, all of these clients could be experiencing abnormal cortisol responses and may therefore be prone to depression.

Cortisol differences continue into the lifespan in response to early life stress. MacMillan et al. (2009) examined differences in cortisol responses with female youth aged 12 to 16 with and without exposure to childhood maltreatment. The youth with a history of maltreatment demonstrated blunted cortisol reactivity in response to a stressful experience. Disrupted HPA activity was also substantiated by Rao, Hammen, Ortiz, Chen, and Poland (2008). Rao and colleagues examined cortisol reactivity with adolescents with and without depression in response to a stressful situation. Those individuals with

depression had higher overall cortisol levels prior to the stressor and a more exaggerated cortisol reaction in response to the stressor. Thus, this is reflective of the relationship between depression and elevated cortisol. Furthermore, ELS and current chronic stress was also predictive of cortisol levels. Those individuals with a history of ELS and chronic stress had the highest cortisol response (Rao et al., 2008).

The increased reactivity of the HPA axis developed in youth may persist into adulthood and produce an increased risk for depression. Coplan et al. (1996) compared HPA activity in adult bonnet macaques that were reared with predictable and unpredictable maternal care. Results suggested that those primates reared in adverse conditions had elevated CRF activity. Altered HPA activity has also been purported with humans reared in adverse conditions. Carpenter et al. (2007) examined ACTH and cortisol responses with a healthy adult population with and without a history of ELS. The sample participated in a stress inducing situation. Those individuals with a history of ELS had blunted ACTH reactivity to the stressor. Cortisol responses were also blunted and reflected less reactivity between baseline to peak levels. While still suggesting a dysregulation, Heim et al. (2000) reported somewhat contrary results in their study examining HPA reactivity to a stressor. Heim and associates recruited a sample that fell into one of four categories: healthy females without history of childhood physical or sexual abuse or depression; healthy females without a history of childhood abuse yet with depression; healthy females with a history of childhood abuse and without depression; and healthy females with both a history of childhood abuse and depression. In response to stress, the females with a history of abuse and current depression had the highest cortisol reactivity and displayed increased ACTH activity. The second highest cortisol and ACTH response was in the group with a history of abuse. These results suggest elevated HPA axis activity is associated with abuse history.

Most clients will present in counseling as a result of a stressful experience. During these times, it will be important for counselors to examine attachment behaviors, history of ELS, and assess for depression. While many clients may only need help adjusting to the stressor and learning new coping skills for managing stress, individuals with a history of ELS and a disposition for increased cortisol reactivity may be expected to need more long term counseling. For clients with elevated cortisol responses, their feelings, thoughts, and behaviors may not fit the context of the stressor. If this pattern is found, it may be an appropriate time for counselors to examine the clients' interpretation of the stressor. Extreme responses or catastrophizing the experience may be indicative of someone whose HPA activity produces a physiological response that clients interpret as intense feelings of anxiety or depression. These clients may have more difficulty getting past the stressor and returning to a state of homeostasis.

While the research may be somewhat conflicting or confusing, the main message is that HPA activity may be altered in those with a history of ELS. ELS is often associated with increased overall output of HPA activity (Tofoli et al., 2011). In addition, HPA activity may be blunted in response to a stressor or it may be exaggerated to produce hypersecretion of cortisol. The responses to stressors may vary by age. Research conducted by Luijk et al. (2010) and Murgatroyd et al. (2009) at infancy with humans and mice suggested an exaggerated cortisol reaction in response to the stressor. These results were repeated in adolescents by Rao et al. (2008). Even in adulthood, this pattern is also found in both animals and humans (Coplan et al., 1996; Heim et al., 2000). This suggests

that individuals with a history of ELS may have developed a stress response that over responds to stressors. However, blunted HPA activity was also observed at the adolescent age (MacMillan et al., 2009) and in adulthood (Carpenter et al., 2007). The blunted response suggests a sensitization to the HPA activity, perhaps attributed to chronic high exposure of stress hormones. In other words, as individuals continually experience situations that produce a release of stress hormones, they may eventually become immune to the constant flow of cortisol, thus altering overall, daily levels of cortisol. Individual responses in HPA activity may need to be examined when treatment options are considered. It may be important to determine if an individual has normal cortisol responses, elevated cortisol responses, or blunted cortisol responses.

ELS and Antidepressant Effectiveness

Asarnow et al. (2009) assessed treatment differences with adolescents (aged 12-18) who did not experience remission from their depression with SSRI treatment. Participants were randomly divided into four treatment groups: a group that switched to a new SSRI; a group that switched to a new SSRI and added cognitive behavioral counseling; a group that took an SNRI; and a group that used an SNRI and added cognitive behavioral counseling. Individuals who continued to be non-responsive to treatment were those with more severe depression, a history of family conflict, and other comorbid conditions. Individuals with a history of abuse responded more favorably to counseling with medication than medication alone. Perhaps type of trauma is predictive of response to antidepressants. Lewis et al. (2010) examined differences in depressive symptoms by type of trauma (no history of trauma, sexual abuse, trauma, or physical abuse) in four different treatment groups (placebo, cognitive behavior therapy, combination of cognitive behavioral therapy and fluoxetine, and fluoxetine alone). In the group without a history of trauma, the combined counseling and fluoxetine was more effective than counseling alone and placebo. Those with a history of trauma or physical abuse experienced reduction in symptoms with all four forms of treatment. However, no significant results or remission was reported with those with a history of sexual abuse.

While some individuals with a history of ELS may respond to antidepressant treatment, there may be treatment options that are more efficacious. Nemeroff et al. (2003) examined differences in treatment responses with chronic depression and ELS. Participants were randomly assigned to one of three treatment groups: antidepressant (nefazodone, an SARI), counseling, and combined treatment with nefazodone and counseling. Of the participants with a history of ELS, 32.9% in the nefazodone treatment group experienced remission. Of the participants with a history of ELS, 48.3% in the counseling treatment group experienced remission. Of the participants with a history of ELS, 53.9% in the combined counseling and nefazodone treatment group experienced remission. It is important to note that there was no significant difference between the counseling alone and counseling with antidepressants treatment groups, suggesting counseling may be the predictive factor of treatment response. Clearly, some individuals with a history of ELS do respond to antidepressant treatment. What could account for these differences in treatment response? It may not only be ELS that predicts treatment outcomes, but the interaction between one's genes and environmental factors. Xu et al. (2011) examined genetic polymorphisms, antidepressant treatment, and ELS. In a sample of Chinese adults with current depression, a gene (TPH2 SNPs [rs7305115]) was

associated with an interaction response. Individuals with that specific gene were less likely to respond to antidepressant treatment if they had a history of ELS.

In the treatment of individuals with a history of ELS, several important findings related to counseling have emerged. As multiple studies have reported, counseling may be the key to depression remission (Asarnow et al., 2009; Lewis et al., 2010; Nemeroff et al., 2003). In each of these studies, while antidepressant was beneficial, it was not as helpful to those individuals who participated in counseling alone or in conjunction with an antidepressant treatment. Furthermore, the type of trauma experienced may predict who responds better to counseling over antidepressant use. This may provide evidence for the cortisol theory of depression when individuals have a history of ELS and for the importance of working through traumas in counseling to help alleviate depressive symptoms.

New Direction for Antidepressants

It is plausible that some individuals with a history of ELS develop glucocorticoid resistance (disruption in the negative feedback system). This phenomenon may not be isolated to individuals with a history of ELS. Rupprecht et al. (1991) treated individuals with and without depression with metyrapone (a substance known to decrease cortisol levels). Results indicated that treatment with metyrapone did not lead to upregulation of cortisol receptors in individuals with depression. Perhaps this is due to, as Dinan (1994) suggested, the plasticity of cortisol receptors may be reduced in individuals with a history of depression. The findings from Rupprecht et al. and Dinan have been confirmed via a meta-analysis conducted by Pariante and Miller (2001). Pariante and Miller noted studies pretreating individuals with depression with dexamethasone (a synthetic glucocorticoid that in healthy populations suppresses cortisol response), consistently report that in individuals with depression, their cortisol response is not suppressed. These results have been interpreted as a malfunctioning feedback system with individuals with depression.

The hormonal response differences may be dependent on receptor binding. Type one cortisol receptors are mineralocorticoid receptors and are located in high concentrations in the cerebellum and hippocampus (Reul, Pearce, Funder, & Krozowski, 1989; Yau & Seckl, 2007). Type two cortisol receptors are glucocorticoid receptors and are more widely distributed in the brain and particularly in the limbic system, including the hippocampus (Reul et al., 1989; Yau & Seckl, 2007). Research related to receptors suggests the type two cortisol receptors are implicated in the stress response and proceeding depression (Dinan, 1994).

Clearly, though, antidepressants are effective for many individuals with depression and a history of ELS. Antidepressants may affect cortisol output. Pariante, Thomas, Lovestone, Makeoff, and Kerwin (2004) articulated that antidepressants may affect the glucocorticoid and mineralocorticoid receptors. Specifically, SSRIs and imipramine (TCA) may suppress neurobiological activity involved in the production of cortisol (Brady, Whitfield, Fox, Gold, & Herkenham, 1991; Kitayama et al, 1988; Pariante & Lightman, 2008). Additionally, Pepin, Govindan, and Barden (1992) found that treatment with desipramine (TCA) may increase the functioning of glucocorticoid receptors. It is hypothesized that the second messenger system activated via the increased serotonin levels is what leads to the normalizing response in HPA activity. It is thought

that many antidepressants may decrease the response of the HPA axis both at rest and when activated (Yau & Seckl, 2007). This may explain the effectiveness of antidepressants with some of those with a history of trauma who respond to antidepressant treatment (Pariante, 2006).

As previously noted, not everyone responds to antidepressant treatment focused on the neurotransmitters dopamine, norepinephrine, and or serotonin. For the individuals for whom antidepressant treatment is ineffective, it may be beneficial to these individuals if antidepressants targeted HPA activity specifically. The effects of current antidepressants on HPA axis activity, and explicitly cortisol, may not be enough for those individuals with a history of ELS to reduce depressive symptoms. Tofoli et al. (2011) suggested that cortisol, including the HPA axis activity, needs to be assessed when treating with antidepressants.

Individuals with depression may respond to medications targeting HPA axis activity. While many antidepressants may alter HPA axis activity, more alterations may be necessary for those individuals with a history of ELS. This may explain the lack of support for antidepressant usage for individuals who report trauma experiences. As previously noted, counseling may be key to reducing depressive symptoms with those with a history of ELS.

Implications for Counselors

The use of antidepressants is widespread; thus, mental health counselors can expect that many of their clients will be using this medication. Mental health counselors are in a critical position where they may be asked to help the client manage his or her medication usage and may also serve as a liaison between the client and the prescribing physician. Therefore, mental health counselors need to be equipped to address client needs and response to antidepressant usage. Because mental health counselors oftentimes meet with their clients on a weekly basis, they are in a prime position to monitor changes that could be attributed to the antidepressant. Counselors should check-in regularly with their clients in order to assess their opinion on how the clients think their medication is working. Other factors to assess on a regular basis may include differences (e.g. less crying, improved sleep patterns, more energy) the client has noted since beginning the medication and the presence of any side effects (e.g. headaches, dizziness, increased anxiety). The goal of treatment is a reduction of symptoms, but not at the expense of side effects that disrupt daily routine. The presence of side effects that overwhelm the client may suggest a dosage change is necessary. It will also be important for the counselor to determine, with the client, if the client is responding positively to the medication or if the client is a non-responder to the medication. If, after consultation with the client, it is determined that the client is a non-responder, it may be necessary for the counselor, client, and prescribing physician to meet to determine the best course of treatment for the client. As not to violate the Health Insurance Portability and Accountability Act (HIPAA), any mutual meeting will need appropriate releases from the client in order to share protected health information.

If a client is a non-responder to antidepressants, it may be important to determine if this could be attributed to HPA axis activity. While it is difficult to determine via talk therapy physiological differences in cortisol output, certain behaviors may suggest

alterations in HPA activity. Exploring with the client how he or she responds in a stressful situation may be indicative of elevated cortisol responses. For example, what happens to the client when he/she is startled? Or how long does it take the client to physiologically calm down (e.g., reduction in heart rate and respiration) after he or she is startled? If clients report they startle more easily than others or take longer to calm down, then perhaps they may be a non-responder due to HPA activity.

If a joint meeting is necessary, certain factors may be imperative to address. Preparation for the meeting may include assessing the etiology of the depression, the client's physiological response to the medication, and the client's preferences for medication usage. Mental health counselors need to be thorough in their intake of background information from the client. Obtaining a thorough history of ELS, including any adverse conditions in childhood, should be a part of all early counseling sessions. Even though many clients may not perceive that events that occurred in childhood are currently affecting them, the occurrence during a critical developmental period necessitates the need for exploration. It cannot be known if these conditions are playing a contributing factor to the current mental health distress; therefore, it is always best to be cautious and assess for ELS.

Mental health counselors also need to explore the client's goals and desires for how he or she wants to alleviate the depression. Clients have the right to choose whether or not to use medication. It will be important to address the physical aspects of medication usage with the client. Under the guidance of the prescribing physician, potential components to address may include what physical differences he or she is noticing since beginning the use of the medication, potential side effects, how to recognize any life-threatening side effects associated with medication usage, any concerns about long-term use of the medication, and how if the client chooses to quit using the medication, it is best to follow the prescribing physician's advice on tapering off the medication. Changing dosages and types of medication may also be necessary for the client dependent upon the client's response to the medication and etiology of depression. Most importantly, the role the mental health counselor plays as the liaison may ensure that the client is heard by the physician.

Conclusion

Antidepressants are the most sought out medication; yet, many individuals do not experience remission from depression with this treatment. Because of the limited symptom reduction reported with antidepressant usage, it is imperative to research the potential reasons why this medication may not be as effective as hoped. One hypothesis gaining empirical support draws from research implicating the role of HPA activity, and specifically cortisol, in the etiology of depression. While not all individuals with depression exhibit disrupted HPA activity, a subset of those with depression do. For those individuals, a history of ELS may be the contributing factor to the disrupted HPA activity and the development of their depression. In order to help all individuals with depression, additional antidepressants may need to be developed.

When clients work with a mental health counselor, the counselor plays a critical role in helping the client to manage his or her medication. A thorough background history evaluating ELS is a necessary component of counseling individuals with depression.

Another central role of the counselor may be to act as the liaison between the client and physician prescribing the antidepressant. The mental health counselor needs to be prepared to meet with both parties, if necessary, and the counselor needs to check in regularly with the client in order to assess how he or she feels the medication is working, among other factors.

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Note: This paper is part of the annual VISTAS project sponsored by the American Counseling Association. Find more information on the project at: http://counselingoutfitters.com/vistas/VISTAS_Home.htm