4-2014

Determining Which Selective Serotonin Reuptake Inhibitor to Choose for the Treatment of Depression with Co-Morbid Conditions

Kristen Manderschied

Determining Which Selective Serotonin Reuptake Inhibitor to Choose for the Treatment of Depression with Co-Morbid Conditions

Kristen Manderschied

Independent Study

University of North Dakota

April 4, 2014

Abstract

Depression is one of the most prevalent disabling diseases affecting millions of people around the world. Many depressed individuals also suffer from co-morbid conditions that complicate treatment of their depression. Joe is a 65 year old male being seen for fatigue and a PHQ-9 score of 10. Initiation of treatment for depression was commenced with the serotonin reuptake inhibitor, sertraline. Selective serotonin reuptake inhibitors (SSRIs) are first line medications for the treatment of depression. Pharmacological and clinical studies have identified slight differences in the profile of each SSRI, giving them unique advantages for use in co-morbid conditions such as anxiety, obsessive compulsive disorder, obesity, insomnia, and cognitive deficits. Many of the SSRIs have been found to be equally efficacious in the treatment of conditions, or conflicting results cannot discern an advantage of one SSRI over another. Sertraline has been found to be the most cost-effective SSRI in the treatment of depression, while escitalopram is the SSRI to be the best tolerated with the least likelihood of causing drug-drug interactions. Choosing the appropriate SSRI for the treatment of depression while considering co-morbid conditions can improve overall outcomes and compliance with the treatment plan.

Background

Depression is one of the most prevalent disabling diseases. It affects millions of people around the world and is one of the most common and widespread of all psychiatric disorders with an estimated lifetime prevalence of major depressive disorder (MDD) of 16.2% (Hindmarch and Hashimoto, 2010; Sanchez, Reines, & Montgomery, 2013; Thaler et al., 2012). Individuals suffering from depression may become withdrawn, feel fatigued, lose interest in usual hobbies, feel hopeless or worthless, have difficulty concentrating, insomnia, change in appetite, thoughts of suicide, and feelings of intense and persistent sadness (www.WebMD.com, 2014). The World Health Organization's Global Burden of Disease project ranked depression as the third leading cause of disease burden worldwide and is estimated to become the leading cause of disability worldwide as prevalence rates continue to rise (2008). Despite the high prevalence, it is estimated that approximately 40%-60% of clinically significant depression is under-recognized and remains untreated or inadequately treated (Calati et al., 2012; Lotrich and Pollock, 2005). The significant unmet therapeutic need in depression is evidenced by increased levels of morbidity and mortality as well as reduced quality of life in individuals with depression and is responsible for up to 850,000 cases of suicide annually (Hindmarch and Hashimoto, 2010). Depression is also one of the most commonly diagnosed chronic illnesses in the elderly population, affecting approximately 11.5% of Medicare beneficiaries with an annual cost of approximately $65 billion. According to the US National Institute of Mental Health, an estimated two million Americans over the age of 65 have a significant depressive illness (Kaplan and Zhang, 2013). Depression is also associated with higher medical co-morbidities, and co-morbid depression has a negative effect on self care, worsening of social and physical

functioning, health status, and increases total medical expenditures (Kaplan and Zhang, 2013; Morris et al., 2012).

Selective Serotonin Reuptake Inhibitors (SSRIs) are one of the first line medication classes utilized in the treatment of depression. The selective serotonin reuptake inhibitors (SSRIs) share the same mechanistic target resulting in higher extracellular levels of serotonin, considered the basis for their antidepressant activity. There is published evidence from pharmacology and clinical efficacy studies that would support meaningful differences among effects of individual SSRIs (Sanchez et al., 2013). Each SSRI has unique advantages for use and taking into consideration co-morbid conditions along with patient needs can improve compliance with the treatment plan and overall health status, social functioning, and physical functioning of the individual.

Case Report

Joe is a 65 year old male patient coming into the clinic today with complaints of fatigue that has increased over the last month; worst over the past week. Joe states he constantly feels fatigued, has no energy to do much of anything for the last couple of months; it has been following a constant course and has been progressing in severity. He denies any change in appetite, recent illness, or difficulty sleeping. He states that his fatigue is unaffected by his work, he feels just as fatigued on his days off from work as he does on the days he does work. Joe has no medical issues to report, family history is positive for hypertension and coronary artery disease, no family history of cancer. He does not take any prescription medications, but takes a multivitamin and Metamucil daily, has no known allergies.

Joe lives at home with his wife, whom he states is very supportive of him and they have a good relationship. He continues to work full time. He is a non-smoker and partakes in 1-2

alcoholic beverages per week on average. Review of systems is noncontributory other than complaints of chronic fatigue as previously mentioned. Vital signs revealed a blood pressure of 134/74, temperature of 98.3 F, respirations of 20, pulse of 68. Physical exam was negative except for a PHQ-9 score of 10. Complete blood count, complete metabolic panel, and thyroid stimulating hormone labs unremarkable.

Because no other source of fatigue could be identified, it is felt Joe is suffering from depression. The plan is to start Zoloft 50 mg oral daily at bedtime for depression. A mental health specialist will be consulted for cognitive behavioral therapy; and they will contact him to arrange an appointment to start therapy. Possible side effects of treatment with SSRIs was discussed with Joe such as GI upset and possible suicidal ideation as the medication takes effect. He will call/return if any suicidal ideation occurs or if he is finding any of the side effects distressing. He will follow up in one month to see how things are going and possible titration of his medication.

Literature Review

When determining which SSRI to prescribe in an individual with depression, the following things should be taken into account in order to promote compliance with the treatment plan: age, cost, co-morbid conditions, and adverse effects of the medication. In the United States there are thirteen second-generation antidepressants (SGAs) approved for treating MDD. Overall, the newer generation antidepressants have similar tolerability profiles and comparative efficacy, with some small differences in risk of specific adverse events (Chemali, Chahine, and Fricchione, 2009; Sanchez et al., 2013). Attempts to establish a hierarchy of SSRIs for MDD have been difficult due to conflicting results between and within studies evaluating these medications.

Currently escitalopram, sertraline and paroxetine are the most commonly prescribed SSRIs (Sanchez et al., 2013). A meta-analysis of 35 trials found escitalopram, sertraline and paroxetine all efficacious when compared with placebo (Sanchez et al., 2013). Numerous trials examining efficacy significantly favored escitalopram and sertraline to those of paroxetine and other antidepressants. Tolerability profiles also favor escitalopram, sertraline, and citalopram over other antidepressants (Cipriani et al., 2009; Sanchez et al., 2013). Paroxetine and citalopram have a higher incidence of sexual dysfunction compared with sertraline, and sertraline is associated with higher incidence of sexual dysfunction than escitalopram (Chemali et al., 2009; Sanchez et al., 2013). In a meta-analysis of ten studies examining antidepressant treatment, escitalopram was reported to have the most favorable treatment effect, response rate, and remission rate compared to all other SSRIs (Sanchez et al., 2013). In a 24 week study with severely depressed patients, escitalopram was more effective than paroxetine at both eight and 24 weeks. Sertraline and paroxetine showed similar low recurrence rates and higher efficacy in studies with longer duration (Andrisano, Chiesa, and Serretti, 2012; Sanchez et al., 2013). Studies have found fluvoxamine and paroxetine to be the least efficacious and acceptable drugs, making them less favorable options when prescribing an acute treatment for major depression (Cipriani et al., 2009). In an eight week head to head comparison study, escitalopram and sertraline showed similar efficacy, response rates, and rates of adverse events (Sanchez et al., 2013). Based on available research, escitalopram and sertraline may be the best choices when starting treatment for moderate to severe major depression because they have the best balance between efficacy and acceptability.

Sleep problems constitute an important set of symptoms in MDD; not only is there a high prevalence of such symptoms in patients presenting with MDD, but in many cases are the main

reason for seeking treatment (Stein and Lopez, 2011; Wilson and Argyropoulos, 2005). The importance of sleep disturbance as a target symptom is exemplified by finding that the majority of MDD patients have at least moderate sleep disturbance at baseline, and that depression tends to be more severe in MDD patients with such disturbances (Gursky and Krahn, 2000; Stein and Lopez, 2011). Previous work on SSRIs has indicated that these are potentially useful in the treatment of sleep disturbances in MDD (Stein and Lopez, 2011).

One 10- to 16- week trial comparing fluoxetine, paroxetine, and sertraline in 125 MDD patients with baseline insomnia, demonstrated that the severity of insomnia and depression all improved to a similar degree among the three medications (Sanchez et al., 2013; Thaler et al., 2012). A second eight week trial comparing escitalopram with fluoxetine in 240 patients with MDD presented response rates with no significant difference detected between the two SSRIs (Thaler et al., 2012). No head-to head evidence demonstrates paroxetine is superior to any SSRI for insomnia with the incidence of insomnia not been found to be significantly different between escitalopram and paroxetine; although, patients treated with escitalopram reported a significantly higher incidence of insomnia than with placebo (Stein and Lopez, 2011; Thaler et al, 2012). There is limited evidence of the comparative effectiveness of antidepressants in treating insomnia in patients with depression, with guidelines reporting conflicting evidence for a single antidepressant or class of antidepressants to be most effective for the treatment of insomnia in patients with depression (Clark, Smith, and Jamieson, 2011). Current literature suggests paroxetine with its sedating profile may not be the best SSRI for the treatment of insomnia as previously believed, but suggests any SSRI could be used for the treatment of depression with co-morbid insomnia.

Another co-morbid condition to consider in the treatment of depression is obesity. Many overweight and obese people suffer from depression with obesity being two to three times more likely among psychiatric individuals than the general population, thus the impact of antidepressant drugs on body weight should be considered whenever therapy is initiated (Boudreau et al., 2013; Serretti and Mandelli, 2010). Certain antidepressants, such as fluoxetine, may reduce body weight while others, such as paroxetine, may increase body weight; however, less evidence is available regarding the long term impact of antidepressants on weight and some associations appear to be transient. There is evidence correlating body weight and severity of depression and any influence of antidepressants on weight may be cause for concern or an opportunity to positively influence obesity while treating depression (Boudreau et al., 2013). On the basis of head-to-head comparative study of MDD patients treated with sertraline or paroxetine, the paroxetine group showed a significantly higher weight gain than the sertraline group (Sanchez et al., 2013). Paroxetine has also been found to have the most significant weight gain over long term treatment than any other SSRI (Deshmukh and Franco, 2003; Serretti and Mandelli, 2010). Other SSRIs used to treat depression have been found to cause some weight loss initially and are more weigh neutral in long term treatment making them a good choice for treating MDD in individuals when affect on weight is a concern. In such cases citalopram, escitalopram, fluvoxamine, fluoxetine, and sertraline may be ideal pharmacotherapy (Boudreau et al., 2013; Serretti and Mandelli, 2010). When choosing a SSRI for the treatment of depression with co-morbid obesity, paroxetine is not an ideal choice.

Cognitive impairment broadly disrupts human behavior and functioning, and is both a cause and a symptom of depressive illness. Cognitive impairment manifests in many ways in patients with MDD including: psychomotor retardation, memory loss, confused thought, risky

decision making, and reduced learning competence, and also appears to be linked to suicidality. Significant neurobiological consequences involving structural, functional, and molecular alterations occur in several areas of the brain during depression. Certain ligands of the sigma-1 receptor are neuroprotective and appear to exert a potent neuromodulatory role in the brain that may have relevance in the response to anxiety and stress, depression, learning, cognition, and antipsychotic activity and have been linked to the improvement of memory and learning processes, depression, anxiety, psychosis, stress, aggression, and pharmacodependence (Hindmarch and Hashimoto, 2010). Affinity of individual SSRIs for sigma-1 receptors varies with fluvoxamine being the most potent, followed by sertraline, fluoxetine, citalopram, and paroxetine (Bhuiyan, Tagashira, and Fukunaga, 2012). Fluvoxamine may have particular benefits in the treatment of patients with severe MDD, those with psychotic depression, those with co-morbid anxiety, and those where any cognitive impairment could well compromise the performance of their everyday tasks or where a risk of cognitive failure would increase non-compliance or raise the risk of accident. A SSRI with sigma-1 receptor agonist activity may have beneficial effects on cognition when compared to an SSRI with no sigma-1 receptor agonist activity; suggesting possible beneficial effects on cognition in dementia with co-morbid depression (Hindmarch and Hashimoto, 2010). Sertraline or fluvoxamine may be good choices for treatment of depression in individuals with cognitive impairment due to their sigma-1 receptor agonist activity.

Major depressive disorder (MDD) is the most prevalent psychiatric disorder affecting up to 4% of all older adults and is associated with increased morbidity and mortality (Calati et al., 2012; Seitz, Gill and Conn, 2010). Recent trials of antidepressant treatments for major depression demonstrate that all available SSRIs are equally efficacious in treatment of older

individuals, have modest effects in late life depression (LLD), and have been reported to have a higher efficacy in comparison to placebo in elderly patients (Calati et al., 2012; Lotrich and Polock, 2005; Seitz et al., 2010).

Several guidelines have recommended citalopram as a first-line treatment for LLD, thus citalopram has been used as a first-line treatment for LLD in clinical practice because it is perceived to be as efficacious and as well tolerated as other antidepressants, with less potential for drug-drug interactions (Seitz et al., 2010). The STAR-D study found depression remission rates of 31% during citalopram monotherapy for trial participants aged 55 years or older, and two additional trials demonstrated limited efficacy of citalopram for LLD or failed to find a significant difference between citalopram and placebo (Chemali et al., 2009; Seitz et al., 2010). Recent meta-analysis of antidepressants for major depression suggest that other potentially suitable first-line treatments for LLD may be better tolerated or more efficacious than citalopram for the treatment of depression. Sertraline has been found to be more effective than placebo in the treatment of depression for older adults in at least two studies, and a study comparing citalopram to sertraline for the treatment of minor depression in older adults found citalopram and sertraline were equivalent in reducing symptoms of depression with similar rates of adverse effects (Seitz et al., 2010). No studies are available comparing escitalopram to citalopram for LLD, although two trials of escitalopram for LLD did not find any significant differences between escitalopram and placebo. A recent meta-analysis of newer antidepressants for the treatment of major depression suggests that sertraline and escitalopram may have the best balance of efficacy and tolerability for initial treatment of major depression (Seitz et al., 2010). Fluoxetine and paroxetine have not been found to be the best choice for elderly individuals due to the increased potential for these medications to induce hyponatremia than other SSRIs

t al., 2009). Also, treatment of LLD can be further comp
of cognitive impairment, co-morbid medical conditions
. Older adults frequently use multiple medications and a
ause of morbidity and mortality making potential drug-
on when selecting any pharmacotherapy for older adults
required to provide improved outcomes for all people su
arch indicates sertraline, escitalopram, and citalopram a
f late life depression.

roximately 60% of individuals experience at least one a
depressant; the risk of adverse events and the possibility
ignificantly as the number of medications increases (Ch
, 2005; Sanchez et al., 2013). Fluvoxamine is a potent in
nd fluoxetine is a potent inhibitor of CYP2D6 and a mo
4 (Lotrich and Pollock, 2005). Paroxetine is a potent inh
n inhibit CYP2C9/19 and CYP2D6 but to a lesser degre
likelihood of causing drug-drug interactions (Sanchez et
ave a lower propensity for drug-drug interactions when
nts based on studies examining in vitro inhibition of P45
scitalopram is metabolized in parallel by at least two CY
nd to lesser extent by CYP2D6), and has little inhibitory
-glycoprotein, thus having a low potential for drug-drug
se of sertraline, escitalopram or citalopram may be prefe
tential for pharmacokinetic interactions in elderly patien

(Chemali et al., 2009). Also, treatment of LLD can be further complicated by the frequent occurrence of cognitive impairment, co-morbid medical conditions and polypharmacy in this population. Older adults frequently use multiple medications and adverse drug events are an important cause of morbidity and mortality making potential drug-drug interactions an important consideration when selecting any pharmacotherapy for older adults (Seitz et al., 2010). Further research is required to provide improved outcomes for all people suffering from LLD, but current research indicates sertraline, escitalopram, and citalopram are acceptable choices for the treatment of late life depression.

Approximately 60% of individuals experience at least one adverse event during treatment with an antidepressant; the risk of adverse events and the possibility of drug-drug interactions increasing significantly as the number of medications increases (Chemali et al., 2009; Lotrich and Pollock, 2005; Sanchez et al., 2013). Fluvoxamine is a potent inhibitor of CYP1A2 and CYP2C19 and fluoxetine is a potent inhibitor of CYP2D6 and a moderate inhibitor of CYP1A2 and CYP3A4 (Lotrich and Pollock, 2005). Paroxetine is a potent inhibitor of CYP2D6 and sertraline can inhibit CYP2C9/19 and CYP2D6 but to a lesser degree than paroxetine, and thus has a lower likelihood of causing drug-drug interactions (Sanchez et al., 2013). Citalopram is believed to have a lower propensity for drug-drug interactions when compared to many other antidepressants based on studies examining in vitro inhibition of P450 hepatic enzymes (Seitz et al., 2010). Escitalopram is metabolized in parallel by at least two CYP enzymes, CYP3A4 and CYP2C19 (and to lesser extent by CYP2D6), and has little inhibitory action against other CYP enzymes or P-glycoprotein, thus having a low potential for drug-drug interactions (Sanchez et al., 2013). Use of sertraline, escitalopram or citalopram may be preferable because of the decreased potential for pharmacokinetic interactions in elderly patients who are taking other

medications when compared to fluvoxamine, fluoxetine, and paroxetine which are more likely to interact with other medications that utilize the CYP450 enzyme system (Chemali et al., 2009). At the time of initiating pharmacological treatments for depression, clinicians should tailor treatment for patient-related factors such as symptoms and potential drug-drug interactions (Seitz et al., 2010). Initiation of antidepressant therapy with an SSRI in an individual on multiple medications, escitalopram is the least likely to cause drug-drug interactions and would be the best choice for treatment in this population.

A current Cochrane review of placebo-controlled SSRI trials in obsessive compulsive disorder (OCD) showed efficacy for all SSRIs included (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) with no statistical differences in short-term therapeutic action noted among the individual SSRIs (Kellner, 2010). Fluvoxamine has been repeatedly shown to be a highly effective treatment for OCD (Aderka et al., 2011). While switching from one first-line drug to another may be advisable, it is still an unresolved issue. One study showed switching from one SSRI to another resulted in a lower response rate (0-20%) than switching from one SSRI to clomipramine (33-40%), while another trial showed a beneficial and relatively rapid response to citalopram in OCD patients resistant to previous oral therapy. SSRIs and the TCA clomipramine are recommended as first-line agents for drug treatment of OCD due to the convincing data from numerous published trials, according to several meta-analyses, current expert guidelines, and consensus statements; but because clomipramine is less well tolerated than SSRIs, SSRIs receive the highest recommendation for treatment of OCD. The current guidelines of the World Federation of Societies of Biological Psychiatry (WFSBP) for the pharmacological treatment of OCD grant the highest category of evidence to the SSRIs escitalopram, fluvoxamine, fluoxetine, paroxetine, and sertraline as well as for the TCA clomipramine, but not

for any other drug. National Institute for Health and Clinical Experience (NICE) of the British Psychological Society and the Royal College of Psychiatrists guidelines indicate the initial pharmacological treatment in adults with OCD should be one of the following SSRIs: fluoxetine, fluvoxamine, paroxetine, sertraline, or citalopram (Kellner, 2010). When choosing an SSRI for the treatment of OCD fluvoxamine has been the mainstay, but research shows there are many SSRIs that may be of benefit if response to fluvoxamine is inadequate.

Anxiety disorders are among the most prevalent of mental disorders, and generalized anxiety disorder (GAD) is the most common impairing anxiety disorder in primary care. Current guidelines for the pharmacological management of GAD recommend first line treatment with an SSRI or pregabalin (Baldwin, Woods, Lawson, and Taylor, 2011; Goodman, 2004). Paroxetine and escitalopram are SSRIs that are approved for the treatment of GAD by the U.S. Food and Drug Administration (FDA) while sertraline, fluoxetine, and fluvoxamine have evidence of anxiolytic effects, have not gained indication for treatment of GAD at this time (Goodman, 2004). Analysis of UK licensed treatments showed SSRIs were found to be the most effective drug treatment option for patients with GAD with escitalopram ranking first in terms of remission while neither fluoxetine nor sertraline have proved efficacy in prevention of relapse (Baldwin et al., 2011). When all active treatments are ranked in terms of remission, fluoxetine was ranked highest, with a 60.6% probability of being the most efficacious treatment and is most effective when patients have experienced a shorter duration of illness (Andrisano et al., 2012; Baldwin et al., 2011). Sertraline is ranked first in terms of tolerability and has been found to be more beneficial on anxiety levels at lower doses, likely because lower doses are less associated with activation symptoms (Andrisano et al., 2012; Baldwin et al., 2011; Goodman, 2004). Paroxetine has been found to be a less effective antidepressant in analysis focusing on anxiety

levels, except in placebo-controlled studies (Andrisano et al., 2012). Escitalopram treatment showed a significantly greater improvement in both anxiety symptoms and depression symptoms than paroxetine or placebo (Sanchez et al., 2013; Stein and Lopez, 2011; Thaler et al., 2012). Paroxetine, fluoxetine, fluvoxamine, and citalopram have an increasing effect on the reduction of anxiety symptoms (Andrisano et al., 2012). According to current research, escitalopram, not paroxetine, may be the best FDA approved treatment for GAD.

Pharmacological options approved by current guidelines for the treatment of panic disorder (PD) include tricyclic antidepressants, benzodiazepines, monoamine oxidase inhibitors, SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs). With little differences among guidelines, SSRIs and the SNRI venlafaxine are currently considered as first line agents for PD patients because of their favorable balance of efficacy and side effects profile. The majority of antidepressants are effective and safe for the short-term treatment of PD. Citalopram is more effective in alleviating panic symptoms if the duration of illness was shorter, while fluvoxamine was not found to be useful for treatment of PD. Andrisano et al, (2012) found that paroxetine was not any more effective than placebo for the improvement in anxiety levels in this group of patients. All antidepressants under investigation with the exception of fluvoxamine were significantly more efficacious that placebo on panic symptoms with the following increasing order of effectiveness: citalopram, sertraline, paroxetine, and fluoxetine (Andrisano et al., 2012). Fluoxetine should be considered as an initial treatment option for individuals with panic disorder.

Costs differ substantially between the three most commonly prescribed SSRIs in the US: escitalopram costs approximately $119 for 30-20mg tablets; and equivalent therapeutic dosage of citalopram costs approximately $27 for 30-40mg tablets; and sertraline costs approximately $16 for 30-100mg tablets (www.drugs.com). Patients using sertraline have been found to have

outcomes that are at least as good as or better than patients using escitalopram or citalopram in terms of adherence, drug costs, and medical spending. Escitalopram patients tend to have lower costs for depression-related non-drug treatment and sertraline patients tend to have lower total medical spending than citalopram patients, but with the exception of drug costs, no differences have been found between escitalopram and sertraline patients. In general, patients who use escitalopram have substantially higher drug costs and worse medication adherence compared to patients who use either citalopram or sertraline. Sertraline is at least as cost-effective as or more cost-effective than the other drugs and is associated with lower drug costs than escitalopram, but not with worse outcomes (Kaplan and Zhang, 2013). The combination of lower drug costs, better adherence, and lower down-stream medical costs indicate that overall sertraline may be the most effective drug to treat depression.

Depression is a serious condition, often accompanied by co-morbid conditions complicating treatment. Serotonin reuptake inhibitors can be used to treat both the depression and co-morbid condition in many cases. Choosing a SSRI that treats both depression and the co-morbid condition can improve compliance and simplify the treatment plan. Sertraline, citalopram, and escitalopram appear to be the most efficacious and best tolerated SSRIs in the treatment of depression and many of its co-morbid conditions.

Learning Points

1. Current head-to-head evidence is not adequate to draw many conclusions regarding the superiority of any agent for the treatment of depression with co-morbid anxiety, insomnia, panic disorder, late-life depression, or cognitive impairment.

2. Escitalopram and sertraline appear to be the most efficacious and tolerated SSRIs for the treatment for a variety of psychological conditions, and can also be beneficial in the treatment of late life depression.
3. Sertraline is one of the most cost effective, efficacious, and tolerable SSRIs available for the treatment of depression.
4. Escitalopram is the least likely of the SSRIs to cause drug-drug interactions and may be the best choice for initiating antidepressant therapy in an individual taking multiple medications.
5. Fluvoxamine or sertraline may be good choices for the treatment of depression in individuals with cognitive impairment due to its activity on sigma-1 receptors.

References

Aderka, I. M., Anholt, G. E., van Balkom, A. J., Smit, J. H., Hermesh, H., & van Oppen, P. (2012). Sudden gains in the treatment of obsessive-compulsive disorder. *Psychotherapy and Psychosomatics, 81*(1), 44-51. doi:10.1159/000329995; 10.1159/000329995

Andrisano, C., Chiesa, A., & Serretti, A. (2013). Newer antidepressants and panic disorder: A meta-analysis. *International Clinical Psychopharmacology, 28*(1), 33-45. doi:10.1097/YIC.0b013e32835a5d2e; 10.1097/YIC.0b013e32835a5d2e

Baldwin, D., Woods, R., Lawson, R., & Taylor, D. (2011). Efficacy of drug treatments for generalised anxiety disorder: Systematic review and meta-analysis. *BMJ (Clinical Research Ed.), 342*, d1199. doi:10.1136/bmj.d1199

Bhuiyan, M. S., Tagashira, H., & Fukunaga, K. (2013). Crucial interactions between selective serotonin uptake inhibitors and sigma-1 receptor in heart failure. *Journal of Pharmacological Sciences, 121*(3), 177-184.

Boudreau, D. M., Arterburn, D., Bogart, A., Haneuse, S., Theis, M. K., Westbrook, E., & Simon, G. (2013). Influence of body mass index on the choice of therapy for depression and follow-up care. *Obesity (Silver Spring, Md.), 21*(3), E303-13. doi:10.1002/oby.20048; 10.1002/oby.20048

Calati, R., Salvina Signorelli, M., Balestri, M., Marsano, A., De Ronchi, D., Aguglia, E., & Serretti, A. (2013). Antidepressants in elderly: Metaregression of double-blind, randomized clinical trials. *Journal of Affective Disorders, 147*(1-3), 1-8. doi:10.1016/j.jad.2012.11.053; 10.1016/j.jad.2012.11.053

Chemali, Z., Chahine, L. M., & Fricchione, G. (2009). The use of selective serotonin reuptake inhibitors in elderly patients. *Harvard Review of Psychiatry, 17*(4), 242-253. doi:10.1080/10673220903129798; 10.1080/10673220903129798

Cipriani, A., Furukawa, T. A., Salanti, G., Geddes, J. R., Higgins, J. P., Churchill, R., . . . Barbui, C. (2009). Comparative efficacy and acceptability of 12 new-generation antidepressants: A multiple-treatments meta-analysis. *Lancet, 373*(9665), 746-758. doi:10.1016/S0140-6736(09)60046-5; 10.1016/S0140-6736(09)60046-5

Clark, M. S., Smith, P. O., & Jamieson, B. (2011). FPIN's clinical inquiries: Antidepressants for the treatment of insomnia in patients with depression. *American Family Physician, 84*(9), 1-2.

Deshmukh, R., & Franco, K. (2003). Managing weight gain as a side effect of antidepressant therapy. *Cleveland Clinic Journal of Medicine, 70*(7), 614, 616, 618, passim.

Goodman, W. K. (2004). Selecting pharmacotherapy for generalized anxiety disorder. *The Journal of Clinical Psychiatry, 65 Suppl 13*, 8-13.

Gursky, J. T., & Krahn, L. E. (2000). The effects of antidepressants on sleep: A review. *Harvard Review of Psychiatry, 8*(6), 298-306.

Hindmarch, I., & Hashimoto, K. (2010). Cognition and depression: The effects of fluvoxamine, a sigma-1 receptor agonist, reconsidered. *Human Psychopharmacology, 25*(3), 193-200. doi:10.1002/hup.1106; 10.1002/hup.1106

Kaplan, C., & Zhang, Y. (2012). Assessing the comparative-effectiveness of antidepressants commonly prescribed for depression in the US medicare population. *The Journal of Mental Health Policy and Economics, 15*(4), 171-178.

Kellner, M. (2010). Drug treatment of obsessive-compulsive disorder. *Dialogues in Clinical Neuroscience, 12*(2), 187-197.

Lotrich, F. E., & Pollock, B. G. (2005). Aging and clinical pharmacology: Implications for antidepressants. *Journal of Clinical Pharmacology, 45*(10), 1106-1122. doi:10.1177/0091270005280297

Morris, D. W., Budhwar, N., Husain, M., Wisniewski, S. R., Kurian, B. T., Luther, J. F., . . . Trivedi, M. H. (2012). Depression treatment in patients with general medical conditions: Results from the CO-MED trial. *Annals of Family Medicine, 10*(1), 23-33. doi:10.1370/afm.1316; 10.1370/afm.1316

Parikh, S. (2009). Antidepressants are not all created equal. *The Lancet, 373*, 700-701. doi:10.1016/S0140-6736(09)60047-7

Sanchez, C., Reines, E. H., & Montgomery, S. A. (2014). A comparative review of escitalopram, paroxetine, and sertraline: Are they all alike? *International Clinical Psychopharmacology,* doi:10.1097/YIC.0000000000000023

Seitz, D. P., Gill, S. S., & Conn, D. K. (2010). Citalopram versus other antidepressants for late-life depression: A systematic review and meta-analysis. *International Journal of Geriatric Psychiatry, 25*(12), 1296-1305. doi:10.1002/gps.2483; 10.1002/gps.2483

Serretti, A., & Mandelli, L. (2010). Antidepressants and body weight: A comprehensive review and meta-analysis. *The Journal of Clinical Psychiatry, 71*(10), 1259-1272. doi:10.4088/JCP.09r05346blu; 10.4088/JCP.09r05346blu

Stein, D. J., & Lopez, A. G. (2011). Effects of escitalopram on sleep problems in patients with major depression or generalized anxiety disorder. *Advances in Therapy, 28*(11), 1021-1037. doi:10.1007/s12325-011-0071-8; 10.1007/s12325-011-0071-8