5-2022

Monotherapy vs. Polypharmacy: SNRIs for the Management of Mood Disorders and Chronic Pain

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by

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A Scholarly Project

Submitted to the Graduate Faculty of the University of North Dakota

in partial fulfillment of the requirements for the degree of

Master of Physician Assistant Studies

Grand Forks, North Dakota

May 2022

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Acknowledgments

I would like to thank my advisor, Professor Jay Metzger, and Professor Mindy Staveteig for their guidance on this project. I would like to thank Marilyn Klug for taking the time to discuss various statistics of this literature review. I also would like to thank Gary Meyers, a pharmacist who discussed the classes of medications studied in this literature review. Lastly, I would like to thank my family for their continued support throughout this program.

Abstract

Chronic pain and mood disorders represent two of the most common disorders managed by primary care providers. Chronic pain management is costly, not only with direct medical costs but through loss of work and productivity. The incidence of mood disorders continues to increase, and disorders such as anxiety and depression coexist with chronic pain in many patients. Meanwhile, polypharmacy presents an increased risk for drug-drug interactions and patient harm. The purpose of this systematic literature review is to explore the potential of reducing polypharmacy in individuals with depression and chronic pain through monotherapy via serotonin-norepinephrine reuptake inhibitors (SNRIs). A literature review was performed using search databases PubMed, DynaMed, and Clinical Key, and Google. The review of the literature revealed that treatment of chronic conditions with multiple medications could result in drug-drug interactions and overdose risks. It was also found that SNRIs have a good safety profile and minimal drug-drug interactions. SNRIs target specific pain pathways to include neuropathic, osteoarthritic, and fibromyalgia pain. These pathways are a different target than nociceptive pain, and therefore SNRIs have the ability to specifically target and treat chronic pain. It was also noted that coexisting chronic pain and mood disorders both occur as either a result of each other or found to coexist incidentally through patient surveys and functional MRI imaging. SNRIs have already been proven effective in the management of depression, and the results of this literature review provide evidence that supports SNRI therapy for the treatment of chronic pain. Therefore, management of chronic pain with comorbid depression via SNRI monotherapy is a valid first approach in an effort to reduce polypharmacy.

Introduction

Chronic pain and mood disorders represent two of the most common disorders managed by primary care providers. Chronic pain management is costly, not only with direct medical costs but through loss of work and productivity. The incidence of mood disorders continues to increase and disorders such as anxiety and depression coexist with chronic pain in many patients. Meanwhile, polypharmacy presents an increased risk for drug-drug interactions and patient harm. This systemic literature review provides information of efficacy for the use of serotonin norepinephrine reuptake inhibitors (SNRIs) for both mood disorders and chronic pain as a monotherapy, potentially reducing polypharmacy risks.

Statement of the Problem

Duloxetine is an SNRI used for the treatment of mood disorders such as depression and anxiety and was the only SNRI approved for the treatment of neuropathic pain. Mood disorders such as depression and anxiety tend to coexist with chronic pain, either resulting in or as a result of chronic pain. Attempts to treat these conditions together with one medication can help reduce the risks posed by polypharmacy.

Research Question

Is treatment for chronic pain and mood disorders best served with monotherapy via SNRIs and antidepressants or by treating each condition separately, posing polypharmacy risk?

Literature Review

The literature review conducted reviews the associated risk factors attributed to polypharmacy and the efficacy of SNRI treatment as monotherapy for chronic pain management in adjunct to mood disorder treatment. A literature review was performed using search databases PubMed, DynaMed, and Clinical Key, and Google. Both keyword and mesh terms were used citing

literature and all searches were filtered to a 5-year time frame, though some studies cited from within the research were found to be no more than 10 years old. The Google search was broad with the keywords “antidepressants and chronic pain.” An article by Sansone published by a peer-reviewed Psychiatry journal and the National Center for Biotechnology Information under the National Library of Medicine provided a literature review for chronic pain management with antidepressant therapy. DynaMed and PubMed searches investigating polypharmacy occurrence and risks provided systematic literature reviews and data collection regarding incidence and populations at risk. Keywords in this search included “polypharmacy, polypharmacy adverse effects, psychotropic polypharmacy, depression,” and a filter to include only studies published within the last five years was used, though further research did cite studies that were no more than ten years old. PubMed searches into SNRI therapy for chronic pain and efficacy for therapy in patients with chronic pain and mood disorders was also conducted. These searches provided systematic literature reviews and random control trials (RCTs) evaluating pain management with antidepressants tricyclic antidepressants (TCAs) and SNRIs, noting reduced effects with SSRI therapy in treatment of pain, though SSRI being first line for depression treatment. Keywords in this search included “SNRI and chronic pain, SNRI chronic pain and depression, chronic pain, antidepressant, and depression.” Again, a filter to include only studies published within the last five years was used, however, a “deep dive” into these searches did produce a literature review within the last ten years, which were also cited. Excluded from this search was literature citing information regarding acute nociceptive pain.

Keywords: SNRI, Chronic Pain, Polypharmacy, Risks, Adverse Effects, Adverse Drug Events, Depression, Anxiety, Serotonin Syndrome, Mental Health Conditions, Psychotropic

Polypharmacy Risks

Polypharmacy is a growing concern in healthcare with many chronic health conditions often requiring multiple medications from different classes to manage a single condition. For instance, it is not uncommon to find hypertension or diabetes mellitus to be controlled by two or more medications. Two other commonly treated conditions are depression and chronic pain. While polypharmacy is most often a risk factor for older adults, the rise in young adults with multiple medical conditions has increased risk in this age group as well (Halli-Tierney et al, 2019). In a systematic literature review conducted by Daniel Safer on Overprescribed Medications for US Adults, he was able to identify the most commonly prescribed medications in the United States to include those medications used for depression and chronic pain (Safer, 2019). As discussed by Rhee and Rosenheck, it is not uncommon to see depression managed by two or more drugs for depression symptoms alone with in-class polypharmacy, between class polypharmacy, or both within class and between class polypharmacy (Rhee & Rosenheck, 2019).

Polypharmacy for chronic conditions poses risks to the patient resulting in adverse drug reactions that have the potential to be life-threatening. Shehab et al. collected data from the National Electronic Injury Surveillance System Cooperative Adverse Drug Event Surveillance project surveying emergency department admissions due to adverse drug reactions. The data included adverse events due to medication errors, overdoses (intentional and unintentional), potentially inappropriate medications for older adults, allergic reactions, and secondary effects such as choking or site reactions (Shehab et al., 2016). Of the top medications noted in this study, antidepressant-related adverse reactions were greatest in the six to 18-year-old age group, and the opioid analgesic adverse reactions were most noted in the 20 – 34-year-old age group (Table 4, Shehab et al., 2016). While antidepressant and opioid analgesic medications did not make up the

most common adverse event medications, they definitely do pose an impact on this type of emergency department visits, not only resulting in patient harm but increasing cost and supply burden to the healthcare system.

With patients taking more than four prescribed medications, it is recommended that their medication list is routinely reviewed, and the addition of more medication is avoided without at least evaluating options for deprescribing another medication first (Halli-Tierney et al., 2019). This recommended practice led me to consider the application of SNRIs for the treatment of both chronic pain and depression with one medication rather than using multiple medications. After continued research regarding polypharmacy with depression management, citing failure to successfully treat depression as reason for in class polypharmacy, between class polypharmacy, or both, it is reasonable to consider the application of SNRI as augmentative depression therapy while also managing chronic pain symptoms.

SNRI Chronic Pain Treatment

Chronic pain, including fibromyalgia, musculoskeletal pain, and neuropathic pain, often coexists with depression. It has been found that chronic pain can result from depression or cause depression, as well as one condition enhancing the severity of the other (Sansone & Sansone, 2008). Because of this coupling of conditions, treatment of both with antidepressants poses potential benefits and reduction in polypharmacy risk. Tricyclic antidepressants (TCAs) pose the most risk for adverse effects while selective serotonin reuptake inhibitors (SSRIs) have been demonstrated as having low efficacy for treatment of chronic pain. This leaves the SNRIs, most notably duloxetine, as the drug of choice for treating chronic pain. Management of chronic pain with antidepressants is not entirely understood, but it is believed it is accomplished by targeting “the noradrenergic descending inhibitory system to inhibit chronic pain.” (Hayashida & Obata,

2019). This mechanism of action is different from the nociceptive target for acute pain and is believed to be why antidepressants can exert an effect on chronic pain. Hayashida & Obata's review of chronic pain treatment includes literature reviews and animal studies investigating the antidepressant effects on chronic pain stating, "the main mechanism of antidepressants that inhibit neuropathic pain is to increase noradrenaline in the spinal cord. Dopamine and 5-HT are also increased by antidepressants in the spinal cord and may enhance the inhibitory effects of noradrenaline in an auxiliary manner." (Hayashida & Obata, 2019). They note that the number needed to treat (NNT) indicates the efficacy of treatment in an inverse measurement. SNRIs had NNTs of 5.0 while SSRIs had NNTs of 6.8, demonstrating more effective treatment outcomes with SNRIs vs. SSRIs.

The review of duloxetine (an SNRI) in the treatment of chronic pain by Pergolizzi et al, included studies which reviewed using SNRIs for treatment of diabetic neuropathy, fibromyalgia, and osteoarthritis/low back pain. The patients in these studies all demonstrated improvement of chronic pain with duloxetine over placebo (Pergolizzi et al, 2013). Pergolizzi et al. discuss the pharmacokinetics of duloxetine, noting the only "special dose recommendations" for duloxetine include those with hepatic or renal disease, which would need dosage adjustment and close monitoring. This supports the greater safety of the drug for chronic pain treatment than that of opioid analgesics. Pergolizzi et al. collected the results from several studies in regard to the efficacy of duloxetine in chronic pain management and individually compared them based on the type of pain (diabetic neuropathy, fibromyalgia, osteoarthritis/low back pain). The results for diabetic neuropathy included a timeline for when analgesic effects started, the safety of drug with CVD, efficacy in older vs. younger patient populations, comparison with TCAs, and comparison against placebo. All results showed favor for duloxetine in treatment for diabetic neuropathy across

both age groups, within one to eight weeks, and better outcomes than TCAs. Similar results were found in studies cited for fibromyalgia and osteoarthritis/low back pain. Unfortunately, this literature review excluded chronic pain conditions that coincided with mental health conditions in an effort to try and facilitate proper chronic pain treatment with duloxetine. Pergolizzi et al. did, however note that "As these pains are often comorbid with major depressive disorder (MDD) and general anxiety disorder (GAD), duloxetine might possess the pharmacologic properties to be a versatile agent able to address several symptoms in these patients." (Pergolizzi et al., 2013).

Chronic Pain and Mood Disorders

Further supporting the understanding of chronic pain and depression coexisting together, Gisev et al. note the combination of opioids and antidepressants being prescribed together (Table 2, Gisev et al., 2019). While the use of antidepressants as an adjunct to chronic pain treatment in individuals with depression and chronic pain was noted to provide increased pain relief, there is a risk for polypharmacy when used in this way. Exploring the ability to treat both conditions with one medication, therefore, reduces polypharmacy and its associated risks. Hooten discusses the relationship between depression and chronic pain, noting the "bidirectional relationship [that] exists between chronic pain and mental health disorders." (Hooten, 2016). Hooten discusses a "3-tier" process for nociceptive pain processing noting regions of the brain that process the pain signal, how the pain is processed, and how emotional and memory processing within the brain is also activated. He supports this with functional MRI imaging of the brain in response to pain, citing the areas of the brain affected and associating them with these three tiers. He discusses that the second and third tiers involve the "inhibitory or facilitatory modulation of incoming nociceptive stimuli," which supports the theory of SNRIs having a mechanism of action that works along the descending pathway (Hooten 2016). The emotional area of the brain stimulated by pain

also is stimulated in patients with depression independent of pain, potentially linking the two conditions in a physiologic way along with patient surveys. Hooten cites surveys of patients rating chronic pain and depression, which supports the relationship of chronic pain and depression through tables, noting the occurrence of each condition within a population. He further compares the incidence of chronic pain resulting in depression or of the depressed individual developing chronic pain. Citing a population-based study, Hooten notes that "participants with mild or disabling neck or low back pain were 2.0 to 2.5 times more likely to experience an episode of depression at 6- and 12-month follow-up than individuals without spinal pain (Caroll et al. 2003)." Hooten also notes that "pain-free individuals with severely elevated levels of depressive symptoms were four times more likely to develop neck or low back pain at six and twelve-months follow-up than individuals with low levels of depressive symptoms (Currie & Wang, 2004)." A large study also found that "participants with 'chronic back pain' were six times more likely to be depressed than pain-free participants. Conversely, pain-free individuals subsequently diagnosed with depression were approximately 3 times more likely to develop chronic back pain than individuals without depression (Currie & Wang, 2004)." With the functional imaging studies and the population-based studies he reviewed, Hooten states that "functional imaging studies support the bidirectional relationship between pain and depression," also noting that this relationship "may be partly mediated by shared neural mechanisms." (Hooten, 2016). Knowing this, it could be assumed that targeting this "neural mechanism" with a single medication could provide the dual effect of antidepressant and chronic pain relief. Sheng investigates the potential of depression causing physiologic changes that promote chronic pain, "chronic pain-induced depression" (Sheng, 2017). Sheng notes that inflammation of the CNS due to depression is responsible for changes of "neurotransmitter metabolism, neuroendocrine function, and neuroplasticity," resulting in chronic

pain. Sheng investigates antidepressants in the treatment of chronic pain-induced depression and notes studies reviewed indicate efficacy in the treatment of both depression and chronic neuropathic pain but fails to note efficacy in promoting mood and decreasing chronic pain with antidepressants as a monotherapy.

Efficacy of SNRI for Monotherapy of Mood Disorder and Chronic Pain

IsHak et al again notes the coexistence of depression and chronic pain. Again, it is believed that the dual neuronal mechanisms of these conditions allow for the treatment of both conditions with an SNRI as a monotherapy (IsHak et al., 2018). IsHak's review also notes a reduction in depressive symptoms as well as chronic pain with the treatment of duloxetine. Sekine et al. studied individuals with major depression and individuals with major depression and chronic pain and the effects of treatment with antidepressants to include SNRIs. They found that both the major depressive group and the major depressive and chronic pain group both had reductions in depression symptoms relatively equally. It was also noted that the group with major depression and chronic pain saw a reduction in both depression and pain symptoms (Sekine et al., 2016). Dharmshaktu et al. notes that tricyclic antidepressants (TCAs) tend to be first line therapy for chronic pain treatment, with SNRIs as second-line treatment for chronic pain. However, SNRIs are as effective in neuropathic pain as TCAs with a smaller side effect profile (Dharmshaktu et al., 2012).

Discussion

Polypharmacy poses significant risks to the patient resulting from overdose and drug-drug interactions. These risks can result in harm as well as increased cost burden on the healthcare system. As discussed by Rhee and Rosenheck (2019), polypharmacy to treat depression alone is not uncommon. Rhee and Rosenheck compared in class, between class, and

both in class and between class polypharmacy groups noting that polypharmacy for depression occurs as a way to "augment" therapy for depression or to treat other psychiatric comorbidities. Since chronic pain and depression are often comorbid conditions, using an antidepressant for chronic pain treatment and depression management can reduce polypharmacy by eliminating other medications used to treat these conditions. Understanding the mechanism of action SNRIs have on chronic pain treatment supports the idea that treatment of chronic pain in a patient with a comorbidity of depression could provide dual effects with one medication. The studies reviewed in this literature review isolate SNRI treatment for chronic pain and show success for treatment of diabetic neuropathy, fibromyalgia, osteoarthritis/low back pain, supporting the theory that SNRIs specifically target neuropathways and thereby inhibit pain. Functional MRI imaging of the brain as it processes pain and the "3-tier" pain processing discussed by Hooten provides a visual of how depression and pain perception share these pathways. However, since chronic pain and mood disorder often coexist, treatment of both conditions with one medication class has the added benefit of reducing polypharmacy.

Application to Clinical Setting

When a patient with chronic pain is searching for options to treat their pain and their depression, prescribing an SNRI for as monotherapy for these conditions can allow for an elimination of at least one drug from their med list. While other antidepressants have also shown efficacy in treating chronic pain symptoms, SNRIs are safer than the TCAs and more studied than the atypical antidepressants. In the event that a depressed patient failing on a depression medication and also has chronic pain, an SNRI can be prescribed as a monotherapy to augment the effects of other medications treating these conditions rather than prescribing additional separate medication

to treat these conditions. By doing so there will decreased risks to that patient which can occur with polypharmacy while improving quality of life by treating both conditions.

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