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Antidepressant Prescriptions Among Hospice Patients During Their Final Days

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By

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ABSTRACT

Depression is frequently experienced at the end of life and can increase pain and suffering. Antidepressants can alleviate depression among the terminally ill; however, many patients have difficulty swallowing oral tablets as death approaches and may be at risk for antidepressant discontinuation syndrome (ADS). This study retrospectively examined antidepressant prescription patterns among 227 hospice patients in a residential care home to determine the extent to which patients were prescribed antidepressants during their final month of life and at what time in the dying process patients may have stopped taking their medication. Results revealed that 67 (30%) of the hospice patients at the care home were prescribed one or more antidepressants. The vast majority (96.1%) of patients did not consume their prescribed antidepressant on their day of death. For those who died at the home, most (62.7%) did not receive their medication during their last 3 days whereas about a quarter of patients (23.6%) stopped receiving their medication 4-7 days prior to their death and a smaller percentage (13.9%) went without medication from 8-34 days prior to death. Records revealed that antidepressants were not consumed during patients' final days for a variety of reasons including difficulty swallowing, minimal consciousness, confusion, nausea, and patient refusal. These results suggest that hospice patients may be at risk for ADS, a factor that could add to suffering during patients' final days. Alternative routes of administering antidepressants at the end of life may be helpful in ensuring that patients are not suffering unnecessarily while they are dying.

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INTRODUCTION

Depression is a common symptom experienced at the end of life, but it also is one that can be particularly difficult to manage in individuals who are dying. While depression has been shown to affect 5%-39% of terminally ill patients (Hotopf et al., 2002; Teunissen et al., 2007), the frequency of severe depressive symptoms increases as death approaches (Tang et al., 2016). Unmanaged depression can decrease quality of life by worsening a patient's physical symptoms. For example, patients with depression have been shown to exhibit higher rates of drowsiness, nausea, pain, dyspnea, poor appetite, and overall worse well-being (Delgado-Guay et al., 2008). Depression in terminal cancer patients has also been associated with immobility, pain, tiredness, and a poor quality of life (Lloyd-Williams et al., 2004). Furthermore, untreated depression can lead to an increased risk of mortality among those with congestive heart failure (Jiang et al., 2001). Given the high rates of depression and the impact on both physical and emotional well-being at the end of life, treatment interventions should be an essential component to high quality hospice and palliative care.

The use of antidepressants can help manage depressive symptoms at the end of life and medication is an effective strategy for lowering rates of depression among those receiving palliative care (Rayner et al., 2011). However, depression in the terminally ill may go undetected or untreated for a variety of reasons. For example, clinicians may fail to detect depression due to a greater focus on physical symptoms like pain and dyspnea, or patients may be unwilling to disclose mental health issues due to stigma. It is also possible that depression is not being treated with antidepressants due to beliefs that depression at the end of life is expected or that there may not be enough time to begin treatment. Concerns about polypharmacy and difficulties patients may have communicating at the end of life may decrease the likelihood of being prescribed

antidepressants while on hospice. Alternatively, patients may receive treatment too late in their illness or their antidepressant may be discontinued as death draws near.

The goal of hospice is to provide emotional, physical, and spiritual support (National Hospice Palliative Care Organization, 2019). Antidepressant prescriptions could be an effective strategy for hospice to manage depression at the end of life. The use of antidepressants has increased over the last few decades, with a reported increase of 400% among all age groups between 1998 and 2008 (Pratt et al., 2011). Antidepressant use has increased among older adults as well. The National Health and Nutrition Examination Surveys (NHANES) found that 14.5% of adults over 60 took antidepressants through 2005-2008 (Pratt et al., 2011), with more recent data revealing increased consumption of 19% of this age group through 2015-2018 (Brody & Gu, 2020). This increase may be due to the rise in production of new medications, greater accessibility to antidepressants, and improved detection and awareness of symptoms.

While antidepressant use has been on the rise for older individuals, this may not be the case for patients receiving hospice care. For example, Shiroma et al., (2011) found that of all patients in a hospice facility, only 11.7% of patients had an antidepressant prescription, a lower rate compared to those over 60 in the general population (Pratt et al., 2011; Brody & Gu, 2020). This low rate of antidepressant use suggests that depression may be going untreated among patients receiving hospice care. Little is known about the use of antidepressants at the very end of life, and practitioners face many challenges that might explain why hospice patients are not receiving antidepressants to manage their depression. Regardless, low rates of antidepressant use may indicate that patients may be suffering unnecessarily as they are dying.

Challenges in Prescribing Antidepressants at the End of Life

Given that patients at the end of life experience a wide variety of symptoms from multiple illnesses, physicians may encounter adverse drug reactions with antidepressants. Patients may be prescribed multiple medications to help manage their symptoms, but some prescriptions can be harmful. Some prescriptions have a high risk of adverse effects compared to their intended benefit. These medications can interact with other prescriptions and lead to hospitalization, greater suffering, and fatality (Lau et al., 2005). Patients who were prescribed a greater number of medications were more likely to be taking a medication with potential adverse effects. McNeil et al. (2016) found the average number of medications prescribed to patients with a prognosis of 12 months or less was 11.5 and this did not include the statin medications they were on to be included in the study. Elderly individuals experiencing adverse effects as a result of a prescription are more likely to be hospitalized and are at a greater risk of death. The risk of hospitalization is also affected by the length one takes the medication; those who take medications longer are more at risk (Lau et al., 2005). Furthermore, some antidepressants are known to have interactions with other drugs that are commonly used at the end of life. For example, monoamine oxidase inhibitors (MAOis) should not be used concurrently with opioids, as the combination can lead to myoclonus and delirium (Breitbart & Jacobsen, 1996). The complexity of drug-drug interactions may influence physicians into prescribing as few medications as possible at the end of life and avoid or discontinue antidepressants.

In addition to the issue of polypharmacy, depression may not be easily detected in terminally ill patients. Physicians may overlook emotional symptoms experienced by the patient as their worsening physical symptoms are the primary concern. The physical symptoms of depression are common symptoms experienced at the end of life, and this makes it difficult to

determine whether patients are simply experiencing symptoms typically present during the dying process. Common symptoms of late-life depression were evaluated by Nelson el al. (2005). The most frequent symptoms experienced and the symptoms that improved the most with treatment were; depressed mood, loss of interest in activities, psychic anxiety, somatic symptoms, decreased energy, somatic anxiety, guilt, insomnia, and suicidal ideation (Nelson et al., 2005).

Clinicians, as well as patients, may expect depression to be a normal part of aging and the dying process. These beliefs may lead practitioners to feel that it is unnecessary to treat depression or that there is nothing they can do. Burroughs et al. (2006) interviewed patients and primary care physicians about late-life depression; they found that both clinicians and patients perceived depression in older adults as justifiable. Furthermore, clinicians felt that there was no need for treatment and that nothing could be done to relieve their suffering, as their depression was caused by isolation and loneliness due to old age (Burroughs et al., 2006). If patients feel that their emotional suffering is to be expected, they mY not speak up to their physicians regarding these issues. Older patients rarely mention their psychological state, as they do not feel comfortable talking about mental issues during a physical examination (Murray et al., 2006). Clinicians may also feel that there is nothing to be done for their patients' late-life depression as their pain is to be expected. This idea held by practitioners may cause them to be less likely to address issues they may notice in their patients, which is necessary because patients will not initiate these conversations.

Antidepressant prescription initiation

One issue that may affect the efficacy of depression management at the end of life is timing- if and when the antidepressant should be started and whether sufficient time is present in which the drug can exert an effect. When antidepressants are prescribed at the end of life, many

patients begin antidepressant treatment within the last two weeks of life. This is not enough time for the treatment to be effective (Lloyd-Williams et al., 1999). Studies examining antidepressant use found that antidepressants show significant superiority over placebo within 4-5 weeks in patients with life-threatening and progressive illnesses receiving palliative care who are not nearing the end of life (Rayner et al., 2011). Initiating antidepressant treatment in those with weeks to live may ultimately do more harm than good, as hospice patients may experience side effects in addition to their current symptomatology. It is possible that older clinicians may be operating under prior research indicating that medications take several weeks before therapeutic effects are observed. It was previously thought that antidepressants take a significant period of time to begin to have an effect in the body. The delayed-onset hypothesis proposed that it would take up to 6-8 weeks after antidepressant initiation to see reduction in depressive symptoms. However, research suggests that this delay may not be as long as previously proposed. For example, Stassen & Angst (1998) found among those who respond to an antidepressant, 70% show improvement within 3 weeks of initiation. In addition, earlier response to antidepressant treatment was associated with a better outcome of overall treatment. Physicians may have difficulty determining the prognosis of a patient which may cause some patients to experience side negative effects without seeing their symptoms improve.

Antidepressant discontinuation

Another challenge when treating depression at the very end of life is that patients may lose the ability to self-administer medication and hospice may decide to discontinue the medication. When antidepressant consumption is suddenly stopped, the patient may experience antidepressant discontinuation syndrome (ADS). ADS occurs across many different classes of antidepressants. Black et al. (1999) reviewed SSRI discontinuation case studies of the general

population and found that the most common symptoms of ADS include dizziness, shock-like sensations, nausea, fatigue, headaches, and insomnia. The majority of patients experienced the onset of symptoms within 1 to 3 days of discontinuation of medication, and all patients experienced symptoms within 2 weeks (Black et al., 1999). Some patients spontaneously recovered from their symptoms, which typically occurred a week after discontinuation, while others found relief 24-72 hours after SSRI medication was reintroduced (Black et al., 1999). When TCAs are terminated abruptly, symptoms include: gastrointestinal and general somatic issues (vomiting, nausea, diarrhea, headaches, fatigue), sleep abnormalities (insomnia, changes in dreaming), parkinsonism, behavioral issues, and anxiety and/or agitation (Zajecka et al., 1997). These symptoms that arise when TCAs are discontinued can begin within 12 hours of the last dose, however, symptoms typically present within the first or second day (Zajecka et al., 1997). Severely ill patients in the intensive care unit (ICU) whose SSRI or SNRI antidepressant prescriptions were discontinued were 3.8 times more likely to experience symptoms of ADS compared to patients who continued antidepressant therapy (Bainum et al., 2017). However, little research has been done on the occurrence of ADS in those who are terminally ill and nearing death. Patients at the end of life are critically ill, therefore, it is likely that hospice patients may be more susceptible to ADS.

The frequency with which antidepressants are discontinued in patients at the end of life is currently unknown. The majority of physicians believe that patients are prescribed too many medications at the end of life, and during the last phase of life, physicians typically discontinue preventative medications first, followed by medications used to treat chronic illnesses like high blood pressure with medications used for symptom management maintained until right before death (Geijteman et al. 2018). While it is unclear where antidepressants would fall, it is possible

that they may be seen as medications to manage chronic illness as opposed to symptoms. Some medications may be terminated due to the patient's wishes. Zeppetella (1999) found that 33% of terminally ill patients consumed fewer medications than they were prescribed. Possible reasons why a patient may wish for their prescription to be discontinued is that they feel the medications are ineffective or they are concerned about and want to avoid negative side effects (Zeppetella, 1999).

Another possibility for the lack of taking medications at the end of life is that patients are no longer able to swallow oral tablets. As patients approach death and become weaker, they may have a hard time swallowing (Ellershaw & Ward, 2003). Ellershaw & Ward (2003) suggest that one of the primary goals of the physician when their patient is in the dying phase is to reevaluate medications. Prescriptions for symptom management, like opioids, anxiolytics, antiemetics, and drugs to manage respiratory secretions are considered essential and often converted to non-oral routes as the patient becomes weaker while other “non-essential” medications, including antidepressants, are commonly terminated (Ellershaw & Ward, 2003). Antidepressants do not frequently come in forms that are suitable for those actively dying, therefore the discontinuation of many medications may be due to the lack of availability in forms other than oral tablets.

Antidepressants to treat common symptoms at the end of life

Antidepressants are also effective in treating other common end of life symptoms, such as pain and anxiety. Pain is among one of the five most common symptoms experienced by those with terminal cancer (Doorenbos et al., 2006). Tricyclic antidepressants (TCAs) have been shown to have analgesic effects (Lynch, 2001) and some selective norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine and duloxetine as well as atypical antidepressants, such as bupropion, are known to be effective in managing chronic neuropathic pain (Sansone & Sansone,

2008). Different SSRI medications are effective in treating different types of pain, such as tension headaches, osteoarthritis, post-stroke pain, chest pain, and diabetic neuropathy. While SSRIs have shown some effective analgesic properties, TCAs and SNRIs are thought to be more effective, especially in treating chronic and neuropathic pain (Haleem, 2019). The mechanism at which antidepressants exert analgesic effects is unknown. The effects on serotonin and norepinephrine in the spinal pain pathways could account for these analgesic properties; however, another possibility is that antidepressants affect the histamine receptors and modulate sodium channels (Sansone & Sansone, 2008).

Anxiety is also common among patients at the end of life and may be another reason for prescribing antidepressants; 13.1% of patients receiving palliative care meet the diagnostic criteria for an anxiety disorder (Wilson et al., 2007). An even higher percentage experience anxiety as death approaches. For example, Conill et al. (1997) examined symptoms in patients at an overage of 6.5 weeks before death and found that 50.6% of patients reported experiencing anxiety. Symptoms of anxiety are common among those with terminal illnesses, and individuals approaching death may have more anxiety as anxiety often coincides with awareness of mortality (Block, 2006). Unmanaged symptoms of anxiety can cause severe distress and hinder quality of life. Antidepressants are effective for treating anxiety disorders. Balasubramaniam et al., (2019) found antidepressant prescriptions had a significant effect on reducing symptoms among participants experiencing late life anxiety, but that antidepressants are likely to be successful when prescribed with ample time to take effect (Balasubramaniam et al., 2019). While other medications, like benzodiazepines, are effective to manage anxiety, antidepressants may be more effective over longer periods of time. Those with chronic terminal illnesses with longer

prognoses are more likely to be prescribed antidepressants than they are benzodiazepines (Atkin et al., 2017).

Pharmacology of antidepressants

There are five classes of antidepressants: selective serotonin reuptake inhibitors (SSRIs), serotonin/norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and atypical antidepressants (Stahl, 1998a). While there are various theories regarding how antidepressants demonstrate their therapeutic effects, the most common monoaminergic hypothesis suggests that antidepressants act through monoaminergic pathways, and that most classes of antidepressants act by inhibiting the action of reuptake (Stahl, 1998a). The most commonly prescribed antidepressants are SSRIs, which are believed to bind to receptor sites, inhibiting the serotonin reuptake pump and increasing the somatodendritic area by decreasing the transporter's affinity for serotonin (Stahl, 1998a). Consistent use of SSRI medication can lead to desensitization of the somatodendritic autoreceptors (Stahl, 1998b). Autoreceptors are receptors that decrease the firing of serotonin neurons and serotonin release. Activation of these receptors is thought to decrease neuronal firing and, in turn, serotonin availability. As these autoreceptors become desensitized, it disinhibits the firing and increases serotonin activity. Desensitization of the autoreceptors takes a longer period of time, thus leading to the delayed efficacy seen in SSRIs (Stahl, 1998a). SNRIs have a similar mechanism of action to SSRIs, however they act on both serotonin and norepinephrine rather than just serotonin (Stahl, 1998a).

TCAs inhibit the action of norepinephrine and serotonin reuptake, leading to the increased availability of monoamines. TCAs assert this effect by inhibiting membrane transporters that pump extracellular monoamines back into the neuron (Racagni & Popoli, 2008).

Monoamine oxidase inhibitors (MAOIs) also work to increase the availability of monoamines but they work through a different mechanism. MAOIs inhibit the function of the enzymes used to metabolize serotonin, norepinephrine, and dopamine with the effect of increasing the availability of monoamines (Stahl, 1998a; Racagni & Popoli, 2008).

Atypical antidepressants include bupropion, trazodone, and mirtazapine. Bupropion works by acting specifically on the noradrenergic and dopaminergic systems by causing a decreased reuptake of dopamine and norepinephrine (Stahl et al., 2004). This medication lacks serotonergic interactions like other antidepressants (Stahl, 1998a). Mirtazapine exerts its effects on the serotonergic and noradrenergic systems. This effect is due to the α_2-antagonistic properties which affect neurotransmission of serotonin and norepinephrine (Stahl, 1998a). Trazodone exhibits a dual mechanism effect on the serotonergic systems; it acts to inhibit the serotonin transporter and acts as an antagonist of the serotonin 5-HT_2 receptors. Trazodone also has antagonistic effects on adrenergic and histamine receptors (Fagiolini et al., 2012).

Side Effects of Antidepressants

Those who are terminally ill can suffer from a wide array of negative symptoms. While antidepressants may act to treat certain symptoms, such as depression, anxiety, and pain, they can also cause negative side-effects and contribute to a dying individual's suffering. However, side effects are present with any medication, and the possibility of side effects should not deter antidepressant usage when needed, as they can improve quality of life. Negative effects of antidepressants differ between classes, but there are general effects associated with all types. Coupland et al. (2011) found that among older patients, consumption of any type of antidepressant was associated with increased risk of falls, mortality, suicidal ideation, self harm, fractures, and gastrointestinal bleeding (Coupland et al., 2011). In addition to these general

side-effects, different antidepressants can exert side effects with differing severity. SSRIs are commonly used, especially in those at the end of life, because of their tolerability. While they may cause headaches, gastrointestinal issues, and an increased risk of falling in older adults, they are typically well-tolerated and do not cause severe effects that have been reported with other classes of antidepressants (Stahl, 1998; Coupland et al., 2011).

TCAs and other antidepressants with muscarinic, adrenergic, and histaminergic effects can also cause significant negative side effects (Racagni & Popoli, 2008). TCAs can cause constipation, dry mouth, urinary retention, altered vision, and confusion, and they have also been associated with higher risk of suicidal ideation and self harm (Coupland et al., 2011). Those who are older are more susceptible to experience confusion and delirium as a side effect (Ahmed, 2019). In addition, TCAs should be avoided if the patient has a history of heart conditions or abnormalities (Ahmed, 2019).

The effects of atypical antidepressants differ depending on the type. Trazodone is an atypical antidepressant that has serotonergic effects as well as strong sedative properties, and is therefore used to treat insomnia, a common symptom experienced at the end of life. A study examining the effectiveness and side-effects of the TCA amitriptyline and trazodone in an elderly population found that while both antidepressants were equally effective in treating depression, trazodone was associated with fewer side effects (Altamura et al., 1989). While trazodone may be a better option compared to TCAs in those worried about side-effects, the properties of trazodone increase one's risk for falls. Because this medication binds to $alpha_1$-adrenoceptors, it may cause orthostatic hypotension making this medication risky to prescribe in patients already at risk for falling (Breitbart & Jacobsen, 1996). Bupropion, another commonly used atypical antidepressant, is usually well tolerated and associated with fewer side

effects. While Bupropion may cause dry mouth, nausea, or insomnia, it lacks common side-effects seen in other medications, like sexual dysfunction, weight gain, and sedation (Stahl et al., 2004). The lack of sedative effects seen in other antidepressants, may render Bupropion beneficial to elderly or terminally ill to reduce the risk of falls.

Prescribing antidepressants in those with complicated medical histories and an array of symptoms can be challenging for physicians. Like any medication, antidepressants can have side effects; however, the possibility of these side effects should not keep physicians from prescribing them to those who need it.

Hospice prescribed antidepressants at the end of life

Understanding the extent to which hospice patients are being prescribed antidepressants at the end of life is difficult to assess. Previous studies have examined depression and antidepressant prescription rates among different populations. For example, of elderly home health care recipients, 13.5% were diagnosed with major depression yet only a small percentage (22%) of those patients were prescribed antidepressants (Bruce et al., 2002). In a study of terminal cancer patients, 22% were prescribed antidepressants during their last year of life (Brelin et al., 2013). In another study of hospice patients in hospice, it was found that only 11.7% were prescribed antidepressants (Shiroma et al., 2011). However, few studies have examined antidepressant use in patients receiving home care at the end of life. Little is known about the use of antidepressant treatment for those experiencing depression, anxiety, pain, and sleep issues at the end of life among hospice patients. The goal of the current study was to explore the overall use of antidepressants among hospice patients at the very end of life. This exploratory study set out to assess the extent to which antidepressants were prescribed, when they were prescribed, and whether they were administered to patients being cared for in a community-run residential

care home where caregivers documented medications prescribed and administered until the patients' died. This study tracked when antidepressants were prescribed as well as when they were discontinued or when caregivers stopped administering them. Understanding antidepressant use in the terminally ill is necessary to ensure that antidepressants are effectively managing symptoms and that additional suffering is not added during their last days.

METHODS

Antidepressant prescription data was collected through de-identified medication files from hospice patients who were cared for at Schenectady Community Home, Inc., (aka Joan Nicole Prince Home) in Schenectady, NY. A total of. 227 patient records were reviewed from patients who resided at the home between June, 2006 and May, 2020. In order to receive care at the home, all residents met the following criteria: were enrolled in hospice, had a terminal diagnosis with a prognosis of three months or less, had a do not resuscitate order in place, and did not have any extraordinary needs that the non-medical facility could not provide. All residents who were cared for at the home received bedside care by trained informal caregivers (IFC) who served as surrogate family members by providing custodial care, including daily tasks such as laundry, cleaning, and meal preparation, as well as medication administration and emotional support.

Patient records consisted of a hospice intake form, patient medication instruction/administration sheets, resident arrival forms, daily care narratives, hospice update sheets, and caregiver daily narratives. Demographic data such as patient gender, ethnicity, age, diagnosis, risk level, and mental status were acquired through hospice intake form. Information regarding diagnosis was recorded using diagnostic criteria from the National Hospice and Palliative Care Organization. Hospice medications along with regimens were recorded on patient

medication sheets where IFCs also recorded each medication administration along with time and date. Patient date of arrival at the home was indicated on the resident arrival form and the hospice enrollment date was noted in the hospice intake form. The date of death or discharge was determined through the resident admission data forms. The length of stay at the home was calculated by subtracting the day of admission from the day of death, and the length of stay on hospice was determined by subtracting the day of enrollment on hospice from the day of death.

Daily medication logs were reviewed to determine the frequency with which patients were prescribed antidepressants as well as the reason for the prescription as indicated by hospice. The records of those prescribed antidepressants were reviewed to determine the most commonly prescribed class of antidepressants and the most popular antidepressants within each class. Some patients were prescribed more than one antidepressant. In cases where a single patient was prescribed 2 or more antidepressants, all antidepressants were recorded.

In instances where hospice prescriptions lacked a clear reason for the medication, the reason for the medication was recorded as unknown. All reasons for antidepressants were recorded from the medication administration sheets. Occasionally, one antidepressant would serve two purposes, while some antidepressants would have no reason documented.

The frequency and dates of antidepressant administration was also recorded. On the patient medication sheets, IFCs recorded whether the prescription was given to and consumed by the resident each day or if the patient was not given the medication. In order to determine how long the patient was taking the antidepressant, the start date of the prescription was recorded from additional medical records when available. The earliest record of the antidepressant prescription was documented as the start date. When patients did not have any past record of medications, the day of the first dose while in the home was used as the start date. The day of the

last dose was also recorded from the medication administration sheet to determine the number of days between the start date and date of last dose.

The length of time between the day of last dose and death was also investigated. Whether the antidepressant was discontinued by hospice or stopped for other reasons was determined and recorded using the medication administration sheet. The number of days between the final dose of medication and the death of the resident was calculated using the date of last dose and the date of death.

In order to determine possible reasons why antidepressants were stopped before death, caregiver narratives, hospice update sheets, and caregiver daily narratives were reviewed to investigate the reason medications were discontinued or no longer administered to patients.

Patient data was collected using Microsoft Excel and analysed using the IBM Statistical Product and Service Solutions (SPSS) version 27. The Union College Human Subjects Review Committee determined this research exempt as the data collected was from deceased patients and all patient files were de-identified.

RESULTS

Initial analyses were conducted to characterize the hospice patient population that received care at the residential care home between 2006 and 2020. Frequency analyses revealed that the mean age of all participants was 76.46 with a range of 38-101. Patient records revealed that the majority were women (60.4%) compared to men (39.6%). The most common NHPCO diagnosis among patients was cancer (71.4%), followed by circulatory/heart disease (11.5), other (11.0), chronic kidney disease (2.2%), respiratory disease (1.8%), dementia (1.8%), and stroke (0.4%) (see Table 1). The majority of patients died in the home (86%), and the mean length of

stay in the residential care home was 31.45 days, with a range of 0-171 days. The mean length of stay on hospice was 108.4 days, ranging from 3 days to 966 days.

Of all medical records, 30% documented at least one antidepressant prescription during the stay at the residential care home. The mean age of those who were prescribed antidepressants was 75.19. There were more female hospice patients prescribed antidepressants (57.4%) compared to male hospice patients (42.6%), however, chi square analyses found this finding to not be significant ($X^2(1) = .37$, $p = .55$).

The majority of patients who had an antidepressant prescription were only prescribed one antidepressant during their stay in the home (86.8%). Of all patients, 13.2% were prescribed more than one antidepressant: 10.3% were prescribed two and 2.9% were prescribed three. In total, there were 79 antidepressant prescriptions prescribed for 67 patients. The most frequently prescribed antidepressant was Zoloft, which accounted for 22.8% of all prescriptions. Lexapro was the second most commonly prescribed antidepressant (16.5%), followed by Mirtazapine (11.4%) and Trazodone (11.4%) (see Table 2). Over half of all antidepressant prescriptions were SSRIs (56.4%). Atypical antidepressants accounted for 25.6% of prescriptions. SNRIs (11.5%) and TCAs (6.4) were the least common classes of antidepressants (see Table 2). The primary reason for the majority of antidepressant prescriptions was not documented on the medication sheet (41.3%). Depression accounted for 38.8% of the primary reason for prescriptions. Antidepressants were prescribed for sleep in 13.8% of patients, for anxiety in 2.5%, pain in 2.5%, and appetite in 1.3% (see Table 3).

To quantify the amount of time patients were prescribed an antidepressant, frequency analysis was performed. The mean number of days a patient was taking their antidepressant, including those who were prescribed their antidepressant before entering the home, was 51.13

days, with a range from 0-264. For patients who died in the home, the average number of days they received antidepressant medications was 44.7 days. Additionally, for patients who died at the home, the mean number of days between the last antidepressant dose and death of the patient was 4.82 days with a range of 0-34. According to patient medical records, 62.7% had between 0-3 days between the last dose and death, 23.6% had 4-7 days between last dose and death, and 13.9% of patients had between 8-34 days between last dose and death (see Table 4).

The majority of patients (96.1%) had at least one day between the date of their last dose and death. Patients who stopped consuming their antidepressants before death either had their prescription discontinued by hospice or were no longer able to be administered the antidepressant by informal caregivers. The reasons why antidepressants were either discontinued by hospice or no longer given by the informal caregiver varied between patients; however, patients who stopped taking antidepressants typically had some record of difficulty swallowing. For example, one caregiver's note included "attempted pudding with pills, unable to effectively take P.O. Didn't get zoloft." Similarly, hospice frequently documented discontinuation due to swallowing issues; for example, hospice wrote in an update for one patient, "med changes due to patient having pain with movement and unable to swallow, all meds other than comfort meds discontinued." In addition to difficulty swallowing, patients also frequently were unable to take their antidepressant because caregivers could not awaken them. Caregivers frequently reported that medications were missed because they were "unable to rouse" the patient or that the patient was "unresponsive," "minimally conscious," or "asleep." One daily narrative described the patient as being in and out of consciousness. This patient "couldn't take all of the meds" and the caregiver notes indicated that they had to take cymbalta out of mouth.

Less frequently, medications were no longer given because the patient experienced confusion. Caregivers reported putting the medication in the patient's mouth, but the patient was unable to understand how to swallow what was put in their mouth. For example, one daily narrative indicated "attempted meds at 10am, unable to understand they were in mouth." In addition, some patients experienced such bad nausea they could no longer take their medications. Hospice wrote in one update, "informed of continued vomiting--unable to take P.O. meds." In addition, patients would occasionally refuse to take medications. Why patients refused to take all their prescriptions or specific prescriptions was unclear. Within the medical records prior to entry into the home, one patient told their physician they wanted to stop taking Lexapro as the patient thought it was causing hallucinations. There were also scenarios that were seen only once. One patient was on a feeding tube and was prescribed liquid prozac through their feeding tube, but as the patient's condition worsened, it was decided to stop all tube feedings including antidepressant being administered via the tube. Another patient experienced agitation and anxiety so severe that the meds could not be given. Hospice wrote, "staff unable to get the patient to drink her chocolate shake or take her oral meds. Instructed to stop oral meds. Just can't."

DISCUSSION

Depression is a common symptom experienced at the end of life. When left unmanaged, depression can worsen patients' physical symptoms and add additional suffering. For example, when patients with advanced cancer have depressive symptoms, they experience a greater frequency and severity of common end of life symptoms, including drowsiness, nausea, pain, and dyspnea (Delgado-Guay et al 2008). While depression can cause and worsen symptoms, antidepressants are effective medications that can help with symptom management and avoid additional suffering during the last few months of life (Rayner et al., 2011). This study examined

antidepressant prescriptions among hospice patients with a prognosis of three months or less to gain a better understanding of antidepressant use and discontinuation of antidepressant medications at the very end of life.

This study found that 30% of hospice patients were prescribed at least one antidepressant. The rate of antidepressant prescriptions in the current study differed from previous research. Shiroma et al. (2011) retrospectively reviewed medical records of patients in a hospice program and found that 11.7% of patients were prescribed antidepressants (Shiroma et al., 2011). Another study retrospectively examined antidepressant prescriptions in the terminally ill found that 10% of patients had antidepressant prescriptions (Lloyd-Williams et al., 1999). The current study found a rate of antidepressant prescriptions nearly three times higher than past studies. This could be because antidepressant use has increased over the past few decades. The National Health and Nutrition Examination Surveys (NHANES) found that antidepressant prescriptions increased from 7.7% of the total population in 1999-2002 to 12.7% of the total population in 2011-2014 (Pratt et al., 2011).

While overall rates of antidepressant use were higher than that reported elsewhere, this study also found that 40% of patients were prescribed antidepressants for less than 3 weeks. These patients may not have seen the effects of their prescription, as antidepressants may begin to demonstrate their effects as soon as 3 weeks for most people (Stassen & Angst, 1998). The possibility of not being on antidepressants long enough for there to be an effect may be due to an incorrect prognosis. Prognostic uncertainty may make it difficult for physicians to appropriately gauge whether there is time for patients who are at the end of life to derive benefits from being placed on an antidepressant. Patients initiating antidepressant treatment at the end of life who do not survive 3 weeks may never receive benefits from the medication. Given that depression at the

end of life is a common occurrence, it is important that physicians not delay, especially given that physicians often overestimate their patients prognosis (Christakis & Lamont, 2000). Prescribing antidepressants to someone too late during the end of life process could result in patients experiencing negative side effects of the medication without any of the benefits that the medication might bring.

Antidepressants were frequently either discontinued or no longer taken days before death. About one third of patients had their last dose 4 or more days before death, including one patient who did not receive their antidepressant for more than a month before they died. Only two patients took their last dose on the day of death, a finding that suggests that there may have been patients experiencing symptoms of ADS in their final days. Symptoms of ADS can arise relatively quickly depending on the class of antidepressant taken. Black et al. (1999) examined case reports of patients who experienced ADS after they stopped taking their SSRIs and found that most patients experienced symptoms as soon as 1 to 3 days, while nearly all patients experienced symptoms after a week (Black et al., 1999). Abrupt termination of TCAs can cause symptoms within the first or second day (Zajecka et al., 1997). Stopping antidepressants abruptly was a frequent occurrence in the current study. It is possible that as many as 37.5% of patients on antidepressants experienced ADS because they were without their antidepressant for at least 4 days prior to their death.

While it is clear most patients stopped taking their antidepressant as their condition declined, it is less clear why this trend occurred. Documentation of the reasons antidepressants were no longer consumed varied between patients; some patients had no record of discontinuation yet suddenly stopped receiving their doses, other patients had their antidepressant discontinuation noted by hospice but without reason, while other patients had one

or more reasons noted by caregivers on the daily narrative sheet or by hospice on the hospice update sheets.

Patients records reviewed in this study indicated that they were often difficult to rouse or experienced difficulty swallowing which rendered them unable to consume their antidepressants. As symptoms of dysphagia worsen, patients can have difficulty swallowing pills such as oral antidepressants (Ellershaw & Ward, 2003). For these reasons, it is recommended that patients be switched to prescriptions with subcutaneous or sublingual administration routes (Ellershaw & Ward, 2003). While many common drugs at the end of life are available in these versions, antidepressants are often not accessible in buccal, rectal, inhalation, and intravenous routes (Das et al., 2019; Kaminsky et al., 2015). Studies have examined the effectiveness of different routes of administration for a variety of antidepressants, however, most alternative routes of antidepressants are still in experimental phases (Das et al., 2019). Pakyurek (1999) described two case studies using sublingual routes of fluoxetine. In this route of administration, the medication is placed beneath the tongue and directly absorbed into the capillaries. While this route was effective in these case studies, clinical trials have yet to be completed regarding sublingual effectiveness of fluoxetine (Pakyurek, 1999). In addition, transdermal use of fluoxetine, amitriptyline, and doxepin have been experimentally explored; however transdermal fluoxetine and amitriptyline have been found to be ineffective at treating depression and transdermal doxepin was effective in relieving neuropathic pain but not depression (Kaminsky et al., 2015). The FDA has approved some antidepressants in alternate routes, including mirtazapine and selegiline orally disintegrating tablets, selegiline transdermal patch, Spravato (esketamine) nasal spray, and fluoxetine liquid (Das et al., 2019). In the current study, one patient was administered fluoxetine solution through a feeding tube. While oral solutions may be easier for patients

experiencing dysphagia to ingest, it still must be swallowed. In addition, while 11.4% of patients were prescribed mirtazapine, there was no indication of orally disintegrating tablets used. Using fluoxetine oral solution or Mirtazapine orally disintegrating tablets may be beneficial in maintaining medication regimen. Dysphagia is a common symptom at the end of life and affects a patient's ability to receive necessary medications. Without antidepressants in forms for alternate routes of administration available for patients when they do experience difficulty swallowing or unresponsiveness, they may be subjected to additional side effects from ADS while their depression goes untreated.

Some patients refused their medications but the reasons why they did so was unclear. Zeppetella (1999) found that 33% of terminally ill patients reported taking less medications than prescribed due to a belief the medication is ineffective, negative side effects, or fear of negative side effects (Zeppetella, 1999). If patients who are concerned about the side effects of the antidepressant and are unaware of the potential side effects of discontinuing their medication, they (or their caregivers) may decide to forego their medication and suffer unnecessarily. Hospice patients who are prescribed antidepressants and caregivers who assist with the administration of these medications may benefit from additional education regarding the negative effects of sudden discontinuation. Similarly, informal caregivers experience difficulty in administering medication. Lau et al. (2010) examined factors that hindered informal caregivers management of hospice patients medications. A lack of caregiver understanding of medications and complex prescription instructions were two factors that negatively affected informal caregivers ability to manage prescriptions (Lau et al., 2010).

When antidepressant medications were discontinued by hospice, they were often discontinued alongside other medications that were not considered “comfort” medications. For

example, hospice wrote, "discontinue daily meds and continue with meds for comfort purposes," when noting the discontinuation of antidepressants. Similarly, another discontinuation reported on the hospice sheet stated, “discontinue all meds except Fentanyl Patch and start Roxinal…to maintain end of life comfort." Hospice practices like these indicate that antidepressant medications are not considered essential to maintaining comfort at the end of life. Termination of medications that are deemed “non-essential” are typically re-evaluated and discontinued as death approaches (Ellershaw & Ward 2003). Medications used specifically for symptom management are typically used by physicians up until death, while other medications that focus on curing or chronic illnesses are discontinued as the patient begins to decline (Geijteman et al. 2018). One reason antidepressants may not be considered necessary during the last days of life is because they typically only come in the form of oral tablets. Within both the hospice and caregiver notes, it was often noted that patients were unable to swallow oral tablets before they were discontinued. Patients and caregivers may opt to crush medications when dysphagia presents, which can alter the effect of the medication and ultimately be harmful to the patient. While some medications can be crushed and administered safely, other medications cannot be. Medications that are modified release, such as extended release or slow release, should not be crushed (Lau et al. 2018). Many antidepressants are available in modified release versions, including cymbalta delayed release, luvox extended release, paxil controlled release, effexor extended release, and wellbutrin extended release (DeVane, 2003; Garcia-Vásquex et al., 2017). Modified-release forms of medications are created to release the active drug over a specific period of time. By crushing these medications the active ingredient can be released all at once, causing toxic effects (Stubbs et al., 2008). Additionally, drugs that have an enteric coat should not be crushed. An enteric coat covers the surface of the tablet to protect the medication from gastric acid within the

stomach (Stubbs et al., 2008). When these drugs are crushed, the active ingredients can be released too soon or cause gastrointestinal side effects, such as nausea (Stubbs et al., 2008; DeVane, 2003). Some antidepressant drugs contain the enteric coating, such as prozac weekly and paxil controlled release (DeVane, 2003). These issues with administration of oral tablets occur in other prescriptions commonly used at the end of life as well, including medications for pain and anxiety. For example, opioids are available in extended release versions, which should not be crushed. Opioids that are immediate-release, on the other hand, are safe to crush. Additionally, opioids and other medications for pain come in other routes of administration, such as liquid and transdermal patches, allowing for these medications to be continued when patients experience dysphagia (Pergolizzi et al., 2014).

In some scenarios hospice discontinued all oral medications or pills. Given the effects of antidepressant discontinuation syndrome, however, antidepressants should be considered necessary to preserve comfort. Another possibility for the frequency at which patients are no longer administered their antidepressant as they approach death is that hospice and caregivers are more focused on treating anxiety, agitation, and pain. The drugs used to treat these symptoms, such as roxanol and haldol, might be thought as options to replace antidepressants. However, antidepressants can be used to manage multiple symptoms at the end of life. While the majority of patients in this study were prescribed antidepressants for depression, there were other patients who were prescribed antidepressants to help manage other symptoms, such as pain and anxiety. Various classes of antidepressants have been shown to help alleviate pain and anxiety (Sansone & Sansone, 2008; Balasubramaniam et al., 2019). Continuing antidepressant treatment during the final days of life not only manages depressive symptoms and prevents additional suffering caused by ADS, but also may help alleviate pain and anxiety at the very end of life.

Additionally, depression among the terminally ill can go undiagnosed and unrecognized by primary care physicians, hospice, caregivers, and the patient. This can happen for a variety of reasons, for example, clinicians may fail to detect depression due to a greater focus on physical symptoms like pain and dyspnea or patients may be unwilling to disclose mental health issues due to stigma. False beliefs held by physicians may impede the recognition of psychiatric illness among the terminally ill. Some healthcare providers may believe that depressive symptoms at the end of life are normal and to be expected. Patients may experience difficulty communicating as death approaches, leading to difficulty vocalizing their symptoms to their physicians. In instances where depression is detected, patients still may not receive adequate treatment. Some prescribers may believe that there is not enough time to initiate treatment with antidepressants before their death. Other factors that interfere with antidepressant prescriptions at the end of life are concerns about polypharmacy.

There were several limitations to this study. Patient records were maintained by a large number of non-familial caregivers as well as different hospice staff visiting the home; therefore, records were not always maintained consistently across visits or patients. Some information, like the reason for prescription, was documented for some patients and not documented for others. In addition, not all resident files included the date for which patient's antidepressants were begun or reasons why the antidepressant was discontinued or no longer administered limiting the ability to determine if and how long a patient was receiving antidepressants prior to arrival at the home and whether the patient was prescribed previous antidepressants in the past. Another limitation of this study was that it was impossible to determine whether patients suffered symptoms of ADS after they stopped taking their antidepressants. While caregiver notes may have indicated patients were experiencing headaches, dizziness or nausea, these symptoms may have arisen for

a wide variety of reasons. In addition, if patients did experience ADS, some may have had difficulty communicating this information to their caregivers. Therefore, there is no way to determine if patients experienced ADS symptoms or if their symptoms were caused by other aspects of their disease states or the dying process. Furthermore, it was impossible to determine whether there were patients in the cohort who had depression but were not prescribed antidepressant.

Although there were limitations, this study found that antidepressants were commonly prescribed medications among home hospice patients with a prognosis of three months or less. When antidepressants are used among this population, abrupt discontinuation may occur as death approaches and the patient's condition declines. This study found that typical symptoms at the end of life such as dysphagia and lack of consciousness impede patients ability to maintain their antidepressant regimen during the last days of life. This study illustrates the difficulties in prescribing antidepressants in those approaching death and raises concerns that discontinuation of antidepressants may exacerbate suffering during the dying process.

FIGURES AND TABLES

Table 1

Frequency of NHPCO diagnoses among all patients

Diagnosis	N (%)
Cancer	162 (71.4)
Circulatory/heart	26 (11.5)
Other	25 (11.0)
Chronic kidney disease	5 (2.2)
Respiratory	4 (1.8)
Dementia	4 (1.8)
Stroke	1 (0.4)
Total	227

Table 2

Frequency of classes of antidepressants prescribed among patients with one or more antidepressant prescriptions

Antidepressant	N (%)
SSRIs	**44 (56.4)**
Zoloft	18 (22.8)
Lexapro	13 (16.5)
Celexa	7 (8.9)
Paxil	4 (5.1)
Prozac	2 (2.5)
Atypical	**20 (25.6)**
Mirtazapine	9 (11.4)
Trazodone	9 (11.4)
Bupropion	3 (3.8)
SNRI	**9 (11.5)**
Cymbalta	5 (6.3)
Effexor	4 (5.1)
TCA	**5 (6.4)**
Elavil	4 (5.1)
Doxepin	1 (1.3)
Total	79

Table 3

Frequency of reasons documented for antidepressant prescriptions, including antidepressants with more than one reason listed

Reasons for Prescription	N (%)
None	33 (41.3)
Depression	31 (38.8)
Sleep	11 (13.8)
Anxiety	2 (2.5)
Pain	2 (2.5)
Appetite	1 (1.3)
Total	80

Table 4

Number of days between the last dose of antidepressant taken and death

Days	N (%)
0-3	32 (62.7)
4-7	14 (23.6)
8-34	7 (13.9)
Total	51

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