Comorbidity of chronic disease and potential treatment conflicts in older people dispensed antidepressants

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Abstract

Objectives: the study aimed to examine the prevalence of comorbidity, the prescribing of potentially inappropriate medications and treatment conflicts in a large sample of older people who have been dispensed an antidepressant medicine.

Methods: a cross-sectional study of administrative claims data from the Department of Veterans’ Affairs, Australia, 1 April–31 July 2007, of veterans aged ≥65 years was conducted. Comorbidities determined using the pharmaceutical-based comorbidity index, Rx-Risk-V. Concomitant medicines that may be potentially inappropriate for patients with depression and areas of treatment conflicts were determined from Australian clinical guidelines or reference compendia.

Results: a total of 39,695 subjects were included, with a median of 5 comorbid conditions (inter-quartile range 3–6). Ninety percent of medicine use was attributed to the treatment of comorbid conditions. Eighty-seven percent of the study cohort was identified as having at least one comorbid condition that may cause a potential treatment conflict when an antidepressant is used. Those conditions of most concern included cardiovascular diseases, anxiety disorders, arthritis or pain management and osteoporosis.

Conclusion: we observed a high level of potentially inappropriate prescribing and treatment conflicts that may arise when caring for older patients dispensed an antidepressant with comorbidity. These have the potential to place a large number of older people with depression at increased risk for adverse events.

Keywords: comorbidity, antidepressant, depression, chronic disease, elderly

Introduction

The lifetime prevalence of depression ranges from 20% in women to 9.6% in men and is one of the leading causes of disability and disease burden globally [1]. By comparison with other chronic medical diseases, depression produces a high health burden and the comorbid state of depression incrementally worsens health more than any other disease combination [2].

In the older population, depression is commonly comorbid with chronic medical disorders. Patients with depression and comorbid disease experience greater morbidity, health service use, expenditure and mortality than non-depressed patients with chronic disease [2, 3]. The associations between depression and chronic diseases are interactive. Depression can delay help-seeking behaviour, reducing the likelihood of detection and diagnosis of other health conditions, and can adversely affect medication adherence and behavioural modifications, to promote health or prevent disease [4]. Conversely, chronic disease increases the risk for depression; the prevalence of depression is three to five times higher in those people with a chronic medical disease.
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than in the general population [2, 3]. This possibly arises from the psychological burden associated with chronic disease, long-term threat of decline in health, increased mortality, disability and pain [4].

The presence of multiple chronic diseases, termed multimorbidity, is common in older persons, with a reported prevalence of 65% [5]. Having multiple diseases is associated with an increased risk for inappropriate prescribing and adverse drug reactions, that may result in an increase in adverse outcomes, such as falls, hospital admission and mortality [6, 7]. The characteristics of specific comorbid conditions can potentially complicate, and impact on, how physicians and patients approach their care relative to their management of depression. The aims of this study were to investigate the prevalence of comorbidity, the prescribing of potentially inappropriate medications and treatment conflicts that physicians may commonly encounter, in a large sample of older people who have been dispensed an antidepressant medicine.

Methods

Study sample

Data were sourced from administrative claims data from the Department of Veterans’ Affairs (DVA), Australia. This database contains details of all prescription medicines, medical and allied health services and hospitalisations subsidised by the DVA, for a treatment population of 310,000 veterans. Medicines are coded according to the World Health Organization anatomical and therapeutic chemical classification and the Schedule of Pharmaceutical Benefits item codes, as previously described [8].

A cross-sectional study was undertaken from 1 April 2007 to 31 July 2007, which included all veterans aged 65 years and over on 1 April 2007, who had an eligible gold card (which entitles veterans to full access to all health services) and who had at least one dispensing of an antidepressant (N06A) medicine. Residential status was classified as either independent or living in residential care facility at study start. Socio-economic status was derived using the socio-economic index for Australia (SEIFA), and comorbidities were determined using the pharmaceutical-based comorbidity index Rx-Risk-V [8].

All analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, NC).

Examination of potentially inappropriate concomitant medicine issues and treatment conflicts

The prevalence of potentially inappropriate medicines and treatment conflicts, for older people dispensed an antidepressant, were determined. This was based on assessment of common comorbid medical conditions for which recommended treatments may contribute additive adverse effects [5] or to specified contraindicated therapies as identified from the Australian Therapeutic Guidelines: Psychotropic [9] and the Australian Medicines Handbook [10]. The final list of identified potentially inappropriate medicines and treatment conflicts by comorbid disease are described in detail in Table 2.

Results

A total of 39,695 subjects (19.1%) had at least one dispensing of an antidepressant from 208,261 veterans aged 65 years or older. Forty-three percent were men and 57% women, with a median age of 83 years (inter-quartile range (IQR) 80–86) (Table 1). The median number of comorbid conditions was 5 (IQR 3–6), and the median number of unique medicines dispensed was 10 (IQR 7–13). Over 90% of the antidepressant cohort were dispensed five or more unique medicines (Table 1).

Table 1 also provides an overview of the number and types of antidepressant medicines dispensed in our study cohort. Most individuals (93.8%) were dispensed only one antidepressant, and selective serotonin reuptake inhibitors (SSRIs) were the most common type of antidepressant dispensed to almost half of the study cohort.

Table 1. Characteristics of older people (≥65 years) dispensed an antidepressant (n = 39,695)

<table>
<thead>
<tr>
<th>Age years (median (IQR))</th>
<th>83 (80–86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (%, male)</td>
<td>43.0</td>
</tr>
<tr>
<td>Residential aged care status (% yes)</td>
<td>21.7</td>
</tr>
<tr>
<td>SEIFAa (% quartiles)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>18.7</td>
</tr>
<tr>
<td>Low–medium</td>
<td>26.8</td>
</tr>
<tr>
<td>Medium–high</td>
<td>24.6</td>
</tr>
<tr>
<td>High</td>
<td>20.9</td>
</tr>
<tr>
<td>Number of comorbid conditions (median (IQR))</td>
<td>5 (3–6)</td>
</tr>
<tr>
<td>Number of unique medicines dispensed (median (IQR))</td>
<td>10 (7–13)</td>
</tr>
<tr>
<td>Prevalence (%) of polypharmacy b (95% CI)</td>
<td>90.7 (90.4–91.0)</td>
</tr>
<tr>
<td>Number of unique antidepressants dispensed (% (95% CI))</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>93.8 (93.5–94.0)</td>
</tr>
<tr>
<td>2</td>
<td>6.2 (5.9–6.5)</td>
</tr>
<tr>
<td>Type of antidepressant dispensed (% (95% CI))</td>
<td></td>
</tr>
<tr>
<td>TCAa (N06AA)</td>
<td>34.0 (33.5–34.5)</td>
</tr>
<tr>
<td>SSRIf (N06AB)</td>
<td>48.6 (48.0–49.1)</td>
</tr>
<tr>
<td>MAOIf (N06AF, AG)</td>
<td>2.3 (2.2–2.5)</td>
</tr>
<tr>
<td>Others (N06AX)</td>
<td>22.1 (21.7–22.5)</td>
</tr>
<tr>
<td>Combinations of antidepressants (% (95% CI))</td>
<td></td>
</tr>
<tr>
<td>TCA and SSRIf</td>
<td>2.0 (1.8–2.1)</td>
</tr>
<tr>
<td>TCA and others</td>
<td>1.0 (0.99–1.1)</td>
</tr>
<tr>
<td>SSRIf and others</td>
<td>1.9 (1.8–2.1)</td>
</tr>
</tbody>
</table>

aIQR, inter-quartile range; SEIFA, socio-economic index for Australia; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor; MAOI, monoamine oxidase inhibitor.

bPolypharmacy is defined as ≥5 unique medicines.
Analysis by comorbidity showed that cardiovascular conditions were highly prevalent in those people dispensed an antidepressant (Figure 1). Almost 60% of the cohort had gastro-oesophageal reflux disease (GORD), 24% had chronic pain, 22% had chronic airways disease, 18% had anxiety and inflammation/pain, which may be indicative of some form of arthritis. Eleven percent were determined to have diabetes and 10% chronic heart failure.

Overall, almost our entire study cohort (87%) was identified as having at least one comorbid condition that may cause a potential treatment conflict when an antidepressant is used. Over two-thirds (35.4%) had three or more comorbid conditions that may cause a potential treatment conflict.

**Potentially inappropriate concomitant medicine issues**

Approximately a third were concomitantly dispensed a benzodiazepine. Eighty-six percent were dispensed a single benzodiazepine, 5.2% were dispensed more than one benzodiazepine and almost 8% were dispensed a long-acting benzodiazepine (Table 2). Of the antidepressant cohort, 61.5% were dispensed another central nervous system (CNS) medicine, with almost a third receiving at least two other unique CNS medicines. Similarly, three-quarters were dispensed an anti-hypertensive and 42% received two or more unique anti-hypertensive medicines. Just less than one-quarter were dispensed an opioid. Over a third of those dispensed a SSRI were concomitantly using a non-steroidal anti-inflammatory drug (NSAID), whilst over half were co-dispensed aspirin (Table 2).

**Comorbid disease treatment conflicts**

In patients with comorbid osteoporosis, an at-risk population for fractures, three-quarters received an anti-hypertensive and almost half were dispensed a SSRI. In patients with diabetes, arrhythmia, ischaemic heart disease or chronic heart failure, approximately one-third were dispensed a tricyclic antidepressant (TCA) (Table 2).

**Discussion**

This large population-based study shows a high level of comorbidity of chronic diseases and associated polypharmacy in older patients dispensed an antidepressant. Further, over 80% of our study cohort had at least one comorbid condition that has the potential to complicate treatment, either due to inappropriate medicine issues or treatment conflicts. The majority of the cohort were prescribed only one antidepressant, with 90% of all medicine use attributed to the treatment of comorbid conditions. Cardiovascular conditions, including hypertension and ischaemic heart disease, were common in our study cohort. This is in accord with the reported association between depression and cardiovascular disease [11]. The comorbid conditions of particular concern, with regard to inappropriate prescribing or treatment conflicts, included cardiovascular diseases, anxiety disorders, arthritis or pain management and osteoporosis. These have the potential to place a large number of older people at increased risk for adverse events.

Almost a fifth of the elderly study population were dispensed an antidepressant, nearly double that commonly reported in other studies [12]. Whilst the study population...
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Table 2. Potentially inappropriate concomitant medicine issues or treatment conflicts in older patients dispensed an antidepressant (n = 39,695)

<table>
<thead>
<tr>
<th>Risk population</th>
<th>Medicine</th>
<th>Reason</th>
<th>Prevalence % (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potentially inappropriate concomitant medicine issue</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressant user, ≥65 years (n = 39,695)</td>
<td>Benzodiazepines</td>
<td>Concomitant use of benzodiazepines may result in increased sedative effects leading to an increased risk of falls, particularly for older patients [10, 18].</td>
<td>n = 14,688 37.0 (36.5–37.5)</td>
</tr>
<tr>
<td>Antidepressant user, ≥65 years (n = 39,695)</td>
<td>≥2 Benzodiazepines</td>
<td>The risk is increased with multiple benzodiazepine use [18].</td>
<td>n = 2,055 5.2 (5.0–5.4)</td>
</tr>
<tr>
<td>Antidepressant user, ≥65 years (n = 39,695)</td>
<td>Long-acting benzodiazepines</td>
<td>The long-acting benzodiazepines should especially be avoided in older patients [10].</td>
<td>n = 3,060 7.7 (7.5–8.0)</td>
</tr>
<tr>
<td>Antidepressant user, ≥65 years (n = 39,695)</td>
<td>Other CNSa medicine (excluding N02B)</td>
<td>≥2 other unique CNS medicines Patients taking two or more CNS medicines have a 2.4–4.5-fold increased risk of falling than those taking one CNS medicine [10, 20].</td>
<td>n = 11,227 28.3 (27.8–28.7)</td>
</tr>
<tr>
<td>Antidepressant user, ≥65 years (n = 39,695)</td>
<td>Anti-hypertensive medicine</td>
<td>Increased risk of orthostatic hypotension and falls with concomitant use of anti-hypertensive medicine particularly in older patients [10]</td>
<td>n = 16,868 42.5 (42.0–43.1)</td>
</tr>
<tr>
<td>Antidepressant user, ≥65 years (n = 39,695)</td>
<td>Opioids</td>
<td>Increased risk of serotonin toxicity with concomitant use of opioids in particular tramadol [9, 10, 24].</td>
<td>n = 2,693 6.8 (5.8–7.2)</td>
</tr>
<tr>
<td>SSRIa user (n = 19,292)</td>
<td>NSAIDsa</td>
<td>SSRIs can reduce platelet serotonin, are associated with increased risk of upper gastro-intestinal bleeding that may be potentiated by concomitant use of NSAID or aspirin [9, 10, 25].</td>
<td>n = 7,303 37.9 (37.2–38.5)</td>
</tr>
<tr>
<td>Comorbid disease treatment conflicts</td>
<td>Anti-hypertensive medicine and osteoporosis (n = 5,020)</td>
<td>Increased risk of hypotension and falls in an at-risk population for bone fracture [10]</td>
<td>n = 3,782 75.3 (74.1–76.5)</td>
</tr>
<tr>
<td>Antidepressant user and osteoporosis (n = 5,020)</td>
<td>SSRIs</td>
<td>SSRIs have been associated with a decrease in bone mineral density and increased risk of fracture [26, 27].</td>
<td>n = 2,458 48.9 (47.6–50.4)</td>
</tr>
<tr>
<td>Antidepressant user and diabetes (n = 4,386)</td>
<td>TCAsa</td>
<td>TCAs can increase blood glucose potentially increasing risk of hyperglycaemia [9, 16].</td>
<td>n = 1,397 31.8 (30.5–33.2)</td>
</tr>
<tr>
<td>Antidepressant user and arrhythmia (n = 2,879)</td>
<td>TCAs</td>
<td>TCAs can have adverse effects on conduction, prolong QT interval, increase heart rate and increase risk of arrhythmia [9, 10].</td>
<td>n = 854 29.7 (28.0–31.3)</td>
</tr>
<tr>
<td>Antidepressant user and IHDa (n = 17,692)</td>
<td>TCAs</td>
<td>TCAs can cause increased heart rate, orthostatic hypotension and conduction abnormalities and are considered relatively contraindicated in IHD [9, 16].</td>
<td>n = 5,966 33.7 (33.0–34.4)</td>
</tr>
<tr>
<td>Antidepressant user and CHFa (n = 5,263)</td>
<td>TCAs</td>
<td>TCAs can cause increased heart rate, orthostatic hypotension and conduction abnormalities and should be avoided in CHF [9, 16].</td>
<td>n = 1,603 30.5 (29.2–31.7)</td>
</tr>
</tbody>
</table>

* CNS, central nervous system; SSRI, selective serotonin reuptake inhibitor; NSAIDs, non-steroidal anti-inflammatory drugs; TCAs, tricyclic antidepressants; IHD, ischaemic heart disease; CHF, chronic heart failure.

Comprises of a large number of war veterans, this may represent overuse. Given the likelihood of treatment conflicts in the study cohort, this should provide impetus for the review and discontinuation of unnecessary therapies.

The presence of multiple chronic diseases increases an individual’s likelihood of having depression [13], and those patients with depression and comorbidity experience worse health outcomes than non-depressed patients [2, 3]. Whilst the prevalence and effects of depression with cardiovascular diseases [11] and diabetes [14] have been well documented, the study of comorbidity of chronic disease with depression as the ‘index disease’ has been less studied. This study provides a valuable overview of comorbidity in an older patient receiving an antidepressant. Together with the potential for comorbid diseases to complicate treatment, the results from this study may facilitate the awareness and consideration of appropriate management options of common comorbid conditions.
Comorbid conditions and treatments to be avoided

Cardiovascular diseases were highly prevalent comorbid conditions in our study cohort and this association and adverse effects on morbidity and mortality in these patients is well documented [11]. Whilst there is some evidence that treatment of depression in patients with cardiovascular disease may reduce morbidity and mortality, the results are equivocal [15]. In terms of safety, TCAs are associated with adverse cardiovascular effects, including orthostatic hypotension, reduced heart rate variability and QT interval prolongation [16]. Approximately a third of those with either arrhythmia, ischaemic heart disease or chronic heart failure were co-dispensed a TCA. Given the use of TCAs in such high-risk patients is associated with a known increased risk of cardiac morbidity and possibly mortality [16], the use of TCAs, where used for depression, should be avoided and other antidepressant therapies used.

Depression and anxiety are commonly comorbid and are associated with more severe symptoms, impairment and subjective distress [17]. In our study, 20% of those dispensed an antidepressant had comorbid anxiety, but of concern is that 40% of the cohort were concomitantly prescribed a benzodiazepine. Benzodiazepines can induce dependence, and are associated with increased risk of sedation, cognitive impairment and risk of falls, particularly in older people. The risk of these side effects is potentiated with concurrent use of antidepressant therapy [18]. All benzodiazepines pose a risk to the older person and their use should be extremely limited.

Comorbid conditions and treatments to be used with caution

CNS active medications, in particular narcotics and antidepressants, are associated with an increased risk of frequent falls and fractures, with an increased risk for fracture ranging from 28 to 76% [19]. The risk of falls is increased with the use of multiple CNS medications. Two or more CNS medicines result in a 2.4–4.5-fold increased risk of falling, compared with those taking only one CNS medicine [20]. All anti-hypertensive medications have the potential to cause orthostatic hypotension and subsequent falls, with the risk increasing with concomitant antihypertensive use and further potentiated by increasing number of anti-hypertensive medications [21]. A large proportion of our study cohort were dispensed at least one other CNS medication or an anti-hypertensive medication, placing a significant number at increased risk for falls. Potential mechanisms that potentiate this risk include dizziness, sedation, orthostatic hypotension, arrhythmias and cognitive impairment. Fracture in older patients, particularly hip fracture, can have serious consequences. Thirty percent of older people who have a hip fracture will subsequently enter long-term aged care institutions, <30% return to the level of functioning before the fracture and there is a 20% increased risk of mortality 5 years post-fracture [22].

Opioids are commonly used for analgesia in moderate to severe pain, and a recent study showed that tramadol and oxycodone are the most commonly prescribed opioids in Australia [23]. Almost a quarter of our antidepressant users were dispensed an opioid, which when combined with an antidepressant causes an increased risk for serotonin toxicity [24]. Serotonin toxicity can vary greatly in severity, but even the mild cases can adversely affect quality of life, particularly for older persons.

Over the last decade, evidence has emerged from case reports and cohort studies that SSRIs are associated with a range of adverse effects [25–27]. This is particularly relevant to older patients, in part due to, increased risk of drug interactions that includes gastro-intestinal bleeding, decreased bone mineral density, falls and fractures [25–27]. Concomitant use of NSAIDs or aspirin and SSRIs can potentiate the risk of upper gastro-intestinal bleeding [25]. We found over half of the antidepressant users in our study were dispensed aspirin and over a third were dispensed a NSAID. Whilst the risk of such adverse events associated with SSRIs may be low, given the widespread use of these medicines, particularly in older people, it is important that physicians are aware of the potential for bleeding risk and monitor accordingly.

Also of concern is the association of SSRIs with decreased bone mineral density [26]. Recent studies have identified a physiologically important role for the serotonergic system in bone physiology and consequently medications that inhibit serotonin transport, such as SSRIs can result in a decrease in bone density [26]. The observed effect size for SSRIs on bone mineral density (a 4–6% reduction) is similar to that of systemic corticosteroids that are well known for their adverse effects on bone density [26]. Daily use of SSRI in adults aged 50 years and older is associated with a 2-fold increased risk of clinical fragility fracture even after adjustment for potential confounders [27]. Almost half of those dispensed a SSRI in our study had comorbid osteoporosis, potentially placing a large number of already at-risk older patients at even higher risk for decreased bone density over time and the increased likelihood of fracture.

Study limitations

A limitation of our study is that we used antidepressant use as a marker of depression and these medicines may not be indicative solely of depression. TCAs for example, when used at low doses, are commonly used to treat neuropathic pain [28] and could account for much of the reported use in the diabetes population. In the current study, the dose of medicines prescribed is not available on the DVA database, so the use of doses to reflect probable indications cannot be determined. However, a recent Australian study found 86% of all antidepressants were prescribed for psychological problems and 71% were prescribed for depression [29]. Whilst psychological therapies are recommended in the treatment of depression, we did not include the association of psychological therapies with comorbid conditions. In the setting of
Comorbid conditions can have a profound effect on managing older patients with depression both in terms of treatment regimens, balancing competing recommendations, and on patients’ ability to manage their self care. This current study highlights the complexity of managing depression in an older patient with comorbidities. The addition of an antidepressant to medication regimens where pain and cardiovascular disease are already being managed puts the population at increased risk of falls, an outcome that may lead to poorer prognosis than hypertension management. Currently, it is unknown how physicians and patients are making decisions about the trade-offs between treat to target for hypertension, depression and falls risk. The importance of treating depression is clear and justified; the issue of concern is how this is integrated with the other physical and mental comorbid conditions and how consequent risks can be reduced. From this study, it is evident that treatment decisions concerning these areas should be addressed in the development of future clinical guidelines for the older comorbid population.

Key points

- Depression, particularly in association with other chronic diseases, has a detrimental impact on many health outcomes.
- Almost 90% of those dispensed an antidepressant had at least one comorbidity that may complicate treatment regimens.
- Comorbid conditions of most concern included cardiovascular disease, arthritis or pain management, osteoporosis and anxiety.

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Conclusions

Comorbidities can have a profound effect on managing older patients with depression both in terms of treatment regimens, balancing competing recommendations, and on patients’ ability to manage their self care. This current study highlights the complexity of managing depression in an older patient with comorbidities. The addition of an antidepressant to medication regimens where pain and cardiovascular disease are already being managed puts the population at increased risk of falls, an outcome that may lead to poorer prognosis than hypertension management. Currently, it is unknown how physicians and patients are making decisions about the trade-offs between treat to target for hypertension, depression and falls risk. The importance of treating depression is clear and justified; the issue of concern is how this is integrated with the other physical and mental comorbid conditions and how consequent risks can be reduced. From this study, it is evident that treatment decisions concerning these areas should be addressed in the development of future clinical guidelines for the older comorbid population.

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