

Overprescribed Medications for US Adults: Four Major Examples

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Abstract

To understand possible medication overprescribing, it would be important to know which classes are the most prescribed, for which indications, for what duration, and for which age groups. Among the 10 most frequently prescribed medication classes for US adults, four were evaluated for overprescribing, and systematically assessed in relation to their primary indication. The assessment included usage patterns, trends, age of recipients, treatment duration, and benefits versus adverse consequences. The findings in this selective review are supported by an extensive search of the medical literature. The four selected medication categories and their most common indication included opioids for chronic pain, proton pump inhibitors for indigestion, levothyroxine for subclinical hypothyroidism, and antidepressants for subsyndromal levels of depression. These medications, grouped by their most frequent indication along with polypharmacy, have experienced major prescription increases in recent years, particularly among older patients. Most concerning is that they have been frequently prescribed for extended periods, usually with inadequate evidence of benefit. High drug usage patterns can aid in quantifying overprescribing within polypharmacy by age group.

Keywords: Polypharmacy; Overprescribing; Opioids; Proton pump inhibitors; Levothyroxine; Antidepressants; Overmedicating

Introduction

Recent surveys in the USA show an increasing degree of prescribed medication treatment [1, 2]. Many of the most commonly prescribed medications have resulted in measurable benefit, which include statin drugs and antihypertensives for cardiovascular disorders.

One would hope that all of the most commonly prescribed drugs and drug classes are the most biologically useful. However, this expectation merits a closer analysis. For example, opioids are a very common medication treatment, and strong

evidence indicates that they are prominently overprescribed. So I reviewed the medical literature to identify the ten most frequently prescribed drugs [2, 3]. These include antihypertensive medications, statin drugs and insulin, drugs that are rarely associated with overprescribing [4, 5]. But there were others listed in the most prescribed top ten whose benefit for their major indication requires careful assessment. These include proton pump inhibitors (PPIs) for gastric/esophageal symptoms, levothyroxine (LTX) for subclinical hypothyroidism (SCH), opioids for relief of chronic pain, and antidepressants for subsyndromal levels of depression. So, I systematically explored the literature to ascertain if these four highly prescribed drug classes are routinely prescribed with benefit for their most common treatment indication.

Most studies on overprescribing emphasize the adverse consequences of high risk and inappropriate drug treatment for vulnerable adults. Such research usually centers on drug interactions with benzodiazepines, non-steroidal anti-inflammatory drugs (NSAIDs), and drugs that are anticholinergic [6, 7]. Their focus is not based on highly prescribed medications or on their inclusion within polypharmacy.

This critical review aims to elucidate to what degree the most common indications for PPIs, antidepressants, opioids, and LTX are medically beneficial, and how such prescribing adds to polypharmacy in older adults.

Literature Search

A literature review was performed using PubMed, Embase, Google, PsycINFO and Web of Science to describe the trends and recent treatment patterns of four of the ten most prescribed medication classes in the USA and of polypharmacy (taking five or more prescribed medications during the prior 30 days). Keywords searched were overprescribing, overmedication, SCH, PPIs, opioids, antidepressants, LTX, and polypharmacy. For simplicity of presentation, LTX is included herein as a class. For the sake of brevity, this critical review focused only on major diagnostic and treatment evidence. It is a selective, not a comprehensive review. Prevalence surveys of US adults taking four very highly prescribed drug classes were assessed to note recent trends. Furthermore, the usage of these medications was identified by age group (e.g. 18 - 44, 45 - 64 and 65 and above) to determine if there were major differences in prescribed medication use with age. The literature survey on these four highly prescribed drugs was then further extended to focus on their relative benefits versus adverse drug events,

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Table 1. Percent of Medication Classes Used by US Adults Aged ≥ 20 Years in 1999 - 2000 and 2011 - 2012 During the Prior 30 Days

Drug category	1999 - 2000	2011 - 2012
SRI antidepressants	4.3	8.5
Levothyroxine	4.6	6.0
PPIs	3.9	7.8
Opioid analgesics	3.8	5.7
≥ 5 co-prescribed drugs	8.2	15

Modified from Kantor et al 2015 JAMA. SRI: serotonin reuptake inhibitors; PPI: proton pump inhibitors.

diagnostic specificity, duration of treatment, and off-label usage.

Literature Review

Medication prevalence data from large government sponsored surveys of US adults are presented in Tables 1 and 2 [1, 2]. The survey findings on Table 1 reveal that the four selected medication classes were highly prescribed (6-9% prevalence) to adults during the prior 30 days in 2011/2012. Also, their use had increased 30-100% between 1999 - 2000 and 2011 - 2012 [1]. The national survey findings on Table 2 reveal that use of these medications increases with increasing age. Adults aged ≥ 65 treated with these four drug classes or within polypharmacy increased two- to 10-fold more than adults aged 18 - 44 years. For U.S. adults aged 65 and over, 15-23% were taking at least one of these selected medication groups and 41% were taking five or more prescribed medications during the prior 30 days [3].

This review provides focused pharmacotherapy information on the major treatment indication of four, highly prescribed medication classes and on polypharmacy. The findings have implications for clinical practice. The relationship between examples of high medication usage, problematic maintenance, and overprescribing has not been discussed as such in the medical literature.

Opioids

Opioids to treat chronic pain represent the case of overprescribing of most concern. Opioids such as hydrocodone and Percocet[®] are useful for the short-term treatment of pain such as that occurring following a recent injury. Also, opioids are relatively safe for short-term use in appropriate oral doses. However, tolerance increasingly develops to the pain reduction effects of these drugs within weeks of use [8]. Consequently, raising the dose becomes necessary to maintain that benefit. Thus, when these drugs are administered at a stable dose over time, they become at best marginally effective to reduce pain [9, 10]. However, increasing the dose and the duration of use creates a heightened risk of dependence and for some addiction [11]. Furthermore, the rapid cessation of maintained opioid treatment or a measurable dose reduction usually leads to

Table 2. Percent of Medication Classes Used in the Prior 30 Days by Age Group in a 2011 - 2014 Survey

Drug group	Age groups (years)		
	18 - 44	45 - 64	Over 65
Antidepressants	8.8	17.5	18.9
Thyroid hormones	2.2	8.1	15.5
PPIs and H ₂ blockers	3.8	14.1	23.2
Opioids and other analgesics	7.0	15.5	16.4
≥ 5 co-prescribed drugs	3.9	18.3	40.7

Data taken from CDC Health, United States, 2016, Trend Tables 79 and 80. H₂: histamine H₂ antagonists; PPIs: proton pump inhibitors.

untoward withdrawal symptoms.

Based on national survey data from 2015, it was estimated that 91.8 million US adults (38.7%) used a prescribed opioid that year (mostly for pain), and an estimated 13.4 million of these adults misused or abused them [12]. Among adults prescribed opioids, 79% were long-term users (> 90 days of use) in 2013 - 2014 compared to 45% in 1999 - 2000 [13]. Opioid use for persistent pain peaks in the elderly [14]. Adverse effects from long-term opioid therapy include constipation (35%), sleep disordered breathing (25%), sexual dysfunction (25-75%), sedation (15%), depression/anxiety (35%) and hyperalgesia [15]. In 2016, prescribed opioids accounted for 17,087 deaths in the USA [16].

PPIs

PPIs such as Prilosec[®] are useful for the treatment of gastric and duodenal ulcers, gastroesophageal reflux disorder (GERD), erosion of the esophageal lining, and a small number of specific gastrointestinal (GI) disorders. They successfully suppress acidity in the stomach [17].

PPIs are approved by the Food and Drug Administration (FDA) for 10 days for the treatment of *Helicobacter pylori*, up to 2 weeks for "heartburn", up to 8 weeks for GERD and for 2 - 6 months for ulcers [18, 19]. Nonetheless, in a community survey, 60% remained on PPIs for over a year and 31% remained on them for 3 or more years [20]. Long-term use of PPIs increases the risk of fractures, gastric polyps, low magnesium levels in the blood, *Clostridium difficile* infections, and anemia [21]. Also, it is hard to discontinue maintained PPI use because 44-59% of patients experience symptomatic withdrawal (which occasionally can last for weeks) after the medication is discontinued [22, 23].

In practice, these drugs are most commonly prescribed by primary care physicians and for the treatment of indigestion [24]. Over 60% of patients taking PPIs do not have a licensed/labeled indication for taking this medication or a documented GI diagnosis [24].

GI disorders such as GERD of course increase with age, but they are also increased in association with smoking, alcohol use, obesity, spicy food, and late meals [25]. So, life pattern changes to reduce GI symptoms can be very useful for treatment.

Levothyroxine (LTX)

LTX is the standard replacement treatment for hypothyroidism, but it is a frequently inappropriate treatment for subclinical hypothyroidism (SCH) [26, 27]. SCH is a diagnosis mainly based on thyroid stimulating hormone (TSH) blood levels mildly above the “normal” laboratory reference range, which is 0.5 - 4.5 mIU/L. The SCH range for TSH is 4.5 - 10 mIU/L [28]. Although the TSH “normal” laboratory range (0.5 - 4.5) represents a population average, it can be quite misleading because levels of TSH consistently and sizably increase with advancing age, particularly for adults over age 60 [29]. Also, TSH levels have been found to increase substantially in relation to region (about three fold), in iodine rich areas (two fold), race, in winter, at night, with morbid obesity, with exercise, during sleep deprivation, with numerous drugs, during pregnancy, and in disorders of the kidney and liver [30, 31]. Thus, it is no surprise that prevalence rates of SCH across studies in community populations range from 3% to 15% [32].

During follow-up assessments of patients with TSH levels from 5 - 10 mIU/L (in conjunction with a normal LTX level), 58-62% diagnosed with SCH reverted to customary age-expected TSH levels within 1 - 3 years [33, 34], although 2-3%/year had levels that then progressed into the hypothyroid range (over 10 mIU/L) [35]. Monitoring elevated TSH levels over time is therefore necessary [33], but not a rush to treatment. Population outcome studies show that LTX treatment for SCH does not alter rates of mortality, depression, quality of life and cognitive function [27, 36].

Furthermore, treating SCH with LTX in the aged can inadvertently lead to overtreatment, increasing the risk of fractures and cardiac arrhythmias [37]. Abruptly stopping LTX can additionally be a problem because it takes many weeks for the body’s feedback endocrine system to reactivate so as to deliver the appropriate amount of thyroxine [38]. LTX treatment adherence varies, but most of those in treatment for 6 or more months continue it for 4 or more years [39-41].

LTX is the most prescribed generic medication in the USA [3]. Like the other frequently prescribed drugs, it clearly has a legitimate use. However, the prevalence of clinically evident hypothyroidism in the USA is estimated to be 0.3-0.8%, whereas the diagnosis of SCH in the USA averages 5% and is expanding [42]. Of late, LTX is often being prescribed more to treat older adults with complaints of fatigue, lethargy, weight gain, cognitive dysfunction, and despondency [43]. In the USA, women are prescribed LTX at a rate over twice that of men [3], even though their TSH levels are similar [44, 45].

Antidepressant treatment

Antidepressant treatment, particularly with serotonin reuptake inhibitors (SRIs), resulted in an additional symptomatic benefit of 25-30% compared to placebo treatment for adults diagnosed with major depressant disorder (MDD) who entered into short-term placebo-controlled clinical trials [46, 47]. Similar degrees of SRI short-term symptomatic benefit have been reported for persons with anxiety disorders [48]. Main-

tenance findings from antidepressant trials are, however, far less supportive. In the sequenced treatment alternatives to relieve depression (STAR*D) project, a very large government-sponsored, randomized clinical trial for adults diagnosed with MDD (n = 2,876), those in remission who entered into a 1-year antidepressant treatment follow-up averaged a strikingly high (34-50%) rate of relapse during that maintenance period [49, 50].

The limitations of antidepressant maintenance are most evident in interview studies of adults ≥ 65 years. In recent systematic surveys, only 15% of adults \geq age 65 years who were taking antidepressants had met criteria for MDD during the prior year [51]. Furthermore in 2011 - 2014, a sizable 27% of persons aged 12 and over who were taking an antidepressant had been doing so for ten years or more [52].

Although MDD was the only categorical diagnosis approved by the FDA for the treatment of unipolar depression, most depressed patients treated with antidepressants experience fewer than the required diagnostic number (five of nine for 2 or more weeks) of MDD symptoms [53-56]. These persons with subthreshold (subsyndromal) depressive symptomatology are, at best, marginal responders to antidepressants [55, 57-59].

Many antidepressants used for long-term treatment increase the risk of impaired sexual function, agitation, weight gain, type 2 diabetes, hypertension, and low bone density [59, 60]. Furthermore, at least 35% of persons who take antidepressants beyond 6 weeks experience unpleasant withdrawal symptoms when the drug is abruptly stopped or its dose is reduced [61, 62].

Polypharmacy

Polypharmacy (taking five or more prescribed medications in the prior month) is particularly common in the elderly. Adults aged ≥ 65 years in the USA represented 13% of the population in 2010 [63], but received 39% of all prescriptions during that year [64]. Of course, adults aged ≥ 65 have more chronic conditions. Specifically, 68% have two or more chronic conditions. These include hypertension (61%), heart disease (32%), arthritis (31%), and diabetes (28%) [65]. Such disorders and metabolic changes occurring with aging obviously account for some of the high medication rate in older adults. Nonetheless, polypharmacy adjusted for these confounds still leads to increased health care costs, more adverse drug events, detrimental drug interactions, increased hospital admissions, cognitive impairment, and more falls [66, 67]. In one large study of adults over age 70, increased odds of adverse drug reactions, when compared to matched patients taking three or fewer medications, were 3.6 for those taking 4 - 6 medications, 4.6 for 7 - 9 medications, and 5.9 for 10 or more [68].

Discussion

This selective literature review supports the proposition that one particularly important place to look for medication over-

prescribing is the most frequently used prescription drugs. As is apparent from this analysis of four highly prescribed medication classes, overprescribing is most common in older adults and in relation to long-term medication treatment. Hopefully, as a result of analyzing the overprescribing of specific highly prescribed drugs, by their major indication, pathways can be identified to better understand the dimensions of polypharmacy and thereby curtail its excesses.

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Conflict of Interest

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Abbreviations

GERD: gastroesophageal reflux disorder; PPI: proton pump inhibitor; FDA: Food and Drug Administration; NSAID: non-steroidal anti-inflammatory drug; LTX: levothyroxine; TSH: thyroid stimulating hormone; MDD: major depression disorder; SRI: serotonin reuptake inhibitor; H₂: histamine 2; STAR*D: sequenced treatment alternatives to relieve depression; SCH: subclinical hypothyroidism; GI: gastrointestinal

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