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RESEARCH ARTICLE

Invisible Victims and the Case for OTC SSRIs

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Abstract
Major depressive disorder is one of the most common serious illnesses worldwide; the disease is also among those with the lowest rates of treatment. Barriers to access to care, both practical and psychological, contribute significantly to these low treatment rates. Among such barriers are regulations in many nations that require a physician's prescription for most pharmacological treatments including selective serotonin reuptake inhibitors (SSRIs). These rules are designed to protect patients. However, such regulations involve a tradeoff between the welfare of "visible" victims, who might suffer negative consequences from a lack of regulation, and the well-being of invisible "victims," who likely experience negative consequences that result from increased barriers to care. This article explores these tradeoffs and argues in favor of shifting SSRIs from prescription-only to over-the-counter status.

Keywords: antidepressants; invisible victims; prescriptions; SSRIs; visible victims

Introduction

Major depressive disorder (MDD) is among the most common serious medical conditions in the world.[1] In the United States, the annual estimated prevalence of MDD is more than 7%, with a lifetime prevalence of more than 14%.[2,3] Starting with the monoamine oxidase (MAO) inhibitor, iproniazid, in 1958, multiple classes of effective antidepressant medications have entered the marketplace including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and selective norepinephrine reuptake inhibitors (SNRIs).[4] However, the vast majority of patients suffering from depression still do not receive any psychiatric treatment at all.[5] This is a problem across continents and in both high- and low-income nations.[6] Only a fraction of those who do receive treatment take medication.[7] Significant barriers to pharmacological therapy include psychological factors such as the stigmatization of the diagnosis and the related fear that "others may find out," as well as practical ones including "inability to pay," "lack of insurance coverage," and limited access to prescribers.[8] The toll of untreated and undertreated depression in economic terms has been placed at more than $326 billion annually in the United States alone.[9] Worldwide, the figure has been estimated to exceed one trillion dollars.[10] Its cost in preventable human suffering remains incalculable. In the wake of the COVID-19 pandemic, the media has increasingly focused on the rise of depression and anxiety as a worsening crisis.[11] Even the White House has identified reducing this burden as a priority.[12] Under such circumstances, taking all reasonable measures to address this ongoing challenge is an ethical and a policy imperative.

Unfortunately, one of the most significant barriers to pharmacological treatment for depression is largely overlooked both in the literature and in public discourse: the requirement that, with the exception of certain complimentary remedies such as St. John's wort, a physician's prescription is required in most nations including the United States, Canada, Great Britain, and throughout Europe to obtain

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antidepressant medication. In the past decade, a small number of experienced psychiatrists including Roy Perlis of Harvard and Dinah Miller of Johns Hopkins have raised the prospect of loosening this requirement, but to most mental health professionals, "the idea of selling [popular antidepressants such as] Prozac or Lexapro over the counter seems unthinkable."[13,14] The dogma that a prescription should be required for antidepressants has not so much been interrogated or investigated as taken for granted. The risks of antidepressant use, including mania and serotonin syndrome, are both real and serious. At the same time, these concerns focus upon visible victims: individuals whose morbidity as a result of antidepressant use will be easily attributable to their medication intake. In contrast, minimal attention has been directed at the invisible victims whose morbidity results from *not* taking antidepressants as a result of either psychological or practical barriers to access. This article examines the ongoing tradeoff between the welfare of visible and invisible victims as it relates to restrictions on SSRIs, the most widely prescribed class of antidepressant medications, and argues for a shift from Rx to over-the-counter (OTC) status for these relatively safe and efficacious drugs. Although the specific regulations examined related to the United States, the broader ethical and policy concerns apply in all nations with similar restrictions.

Over-the-counter medications

In 1938, the Food and Drug Administration (FDA) issued regulations implementing the Federal Food, Drug, and Cosmetic Act (FFDCA) to create a class of nonnarcotic medications that, for the first time in United States history, required a physician's prescription. Prior to that time, American consumers could "consult a doctor and get a prescription"; however, "they were under no obligation to do so" for nonnarcotic drugs.[15] Instead, "[i]f they chose not to, they could go directly to a druggist and buy the drug of their choice." Economist Peter Temin described these regulations as a "stunning change in the way drugs were to be sold" in that the individual consumer was "no longer considered capable of selecting his own drugs."[16] Soon the FDA issues Trade Correspondences that listed specific medications and classes of medications, such as sulfa drugs, aminopyrine and cinchophen, that fell into the prescription-only category.[17] The pharmaceutical industry was itself a driving force behind these restrictions that prevented competitors from bringing products to market.[18] As a result, self-medication was sharply curtailed and the power of physicians as gatekeepers increased.[19] At the same time, the power of pharmacists diminished considerably. Thirteen years later, the Durham–Humphrey Amendment to the FFDCA set forth specific guidelines for classifying drugs as either legend (i.e., prescription-only) medications or OTC medications.[20] The statute required a physician's prescription for "any habit forming drug, any drug so toxic or harmful that it required the supervision of a practitioner for its administration, or any new drug approved under the safety provision of the 1938 act that had to be used under supervision."[21] Controversially, "[r]efills of prescription drugs [also] required the authorization of the prescriber."[22] While the specific regulations have evolved, the overall regularly framework continues to remain in effect to this day.

The vast expansion of the requirement for prescriptions stemmed, at least in part, from concerns over consumer safety. The impetus for the passage of the FFDCA itself was the "Sulfanilamide disaster" of 1937 in which a toxic formulation of sulfanilamide prepared with diethylene glycol ("elixir sulfanilamide") led to an estimated 105 deaths.[23,24,25] Under the Durham–Humphrey Amendment, "any drugs that can cause a habit or be dangerous to a patient must be dispensed by a healthcare provider through a prescription."[26] In contrast, a "drug must be made available without a prescription if, by following the labeling, consumers can use it safely and effectively without professional guidance."[27] Classification as an OTC medication may occur through the new drug application process. Alternatively, rules established by the FDA in 1972 allow for the FDA to review existing drugs for reclassification from legend to OTC status.[28] Although in the decade prior to 1994, the number of medications reclassified from legend to OTC averaged about one annually, the frequency of such shifts has since increased considerably.[29] Well-known examples of medications that have moved from Rx to OTC status include ibuprofen (1984), minoxidil (1996), loratadine (2002), omeprazole (2003), naloxone (2023), and norgestrel (2023).

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The major factors to be considered in the review process include the "benefit–risk comparison, consumer-friendly labeling, and how to make the drug a good choice as an alternative to prescription medication."[30] The FDA itself notes that, "[w]hen considering an Rx-to-OTC switch, the key question for the FDA is whether patients alone can achieve the desired medical result without endangering their safety."[31] No antidepressant medication has made the switch from Rx to OTC status since the review process began in 1972, nor has any manufacturer submitted a successful application for an OTC antidepressant during that time.

Selective serotonin reuptake inhibitors

Although initially developed in the 1970s, SSRIs first became available to American consumers in the late 1980s when Eli Lilly and Company brought Prozac (fluoxetine) to market.[32] In the following decades, another five SSRIs received FDA approval: Zoloft (sertraline) (1991), Paxil (paroxetine) (1992), Luvox (fluvoxamine) (1994), Celexa (citalopram) (1998), and Lexapro (escitalopram) (2002).[33] All are currently available in generic forms, and all, except Luvox, have been approved specifically for the treatment of MDD.[34] At present, SSRIs account for approximately two in three prescriptions for antidepressants in the United States.[35] All SSRIs require a physician's prescription.

The data supporting the benefits of SSRI as a treatment for MDD are robust. SSRIs have been shown to be as effective as TCAs when prescribed for MDD.[36] The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, the "largest and most consequential antidepressant study ever conducted," reported a 39.9% remission rate "with aggressive dosing of citalopram…for up to 14 weeks."[37,38,39] In another major study of multiple SSRIs, "the proportion of patients who met criteria for major depression dropped from 74% at baseline to 32% at 3 months, and 26% at 9 months."[40] While SSRIs do not help all patients, a significant number of patients do achieve meaningful and often life-changing clinical outcomes.

One of the major factors explaining the marketplace dominance of SSRIs is their relative safety profile compared to other classes of antidepressants such as MAOIs and TCAs.[41,42] The most serious risks of SSRIs include possible increased rates of suicide, serotonin syndrome, and mania. All of these are highly concerning outcomes. However, while these consequences are obviously serious, the rates of increased risk remain low. Some of these risks only appear to affect certain populations. For example, the elevated threat of suicide while on SSRIs appears to be limited to adolescents.[43,44] The most common side effects associated with SSRIs, namely "sexual dysfunction, sleepiness, and weight gain," may prove unpleasant but are generally *not* dangerous.[45] Finally, overdose—either with intent to self-harm or through therapeutic misadventure—remains a risk with *any* medication. However, fatal SSRI overdoses are exceptionally rare. Nearly all involve co-ingestions.[46] Even ingestions of 30 times the prescribed daily dose are often asymptomatic or cause only minor symptoms.[47] While the risks of SSRIs should not be dismissed lightly, these dangers ought to be balanced against the potential benefits to be derived from increased access.

Invisible victims

The concept of tradeoffs between visible and invisible victims in healthcare first received widespread attention when Oregon Governor John Kitzhaber, a former emergency room physician, popularized the terminology in the 1990s.[48] "Visible victims" are "individuals whose morbidity or mortality as a result of a particular policy is apparent to themselves or to others."[49] For instance, if Medicaid stopped paying for cadaveric lung transplants in order to fund preventive health measures such as smoking cessation programs, patients refused transplants on economic grounds would see themselves as being short-changed. In Kitzhaber's terminology, they are visible victims. However, the individuals whose smoking cessation is currently not funded, and who later die of undetected lung cancer, likely "do not even conceive of themselves as victims at all."[50] To Kitzhaber, they are invisible victims. The political structure of the American healthcare system often prioritizes visible victims over invisible victims, often

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irrationally, even when prioritizing the interest of invisible victims would significantly lower rates of morbidity and mortality.[51] As discussed below, the tradeoffs involved in the classification of medications as Rx versus OTC may reflect precisely such a systemic bias. A medication that is listed as OTC and subsequently results in injuries or deaths that might have been prevented, had that medication required a prescription, will appear to be a classification error, and those injured or killed will become visible victims. In contrast, a medication listed as Rx-only, leading to patients to suffer morbidity or mortality from diminished access, will likely draw far less notice. Individuals who experience negative outcomes from this lack of access may not attribute these outcomes to barriers or classification errors and often do not conceive of themselves as victims at all. They remain invisible.

The case for reclassification

Reclassifying SSRIs as OTC medications is highly likely to increase use. Jongwha Chang and colleagues have noted that among the "multiple advantages to consumers" that arise "when products are switched from prescription to OTC," one of the most significant is "the ease of access to essential medications."[52] They identify three specific barriers that OTC status is likely to help overcome the time involved in obtaining medication, the cost of acquisition, and the comfort of patients in doing so.[53] Each of these likely plays a role in limiting SSRI access at present. The shortage of psychiatric providers in the United States is severe and worsening.[54] The field is aging rapidly and has been beset with retirements in the wake of the COVID-19 pandemic. New patients may have to wait several months for a psychiatric appointment, while many providers no longer accept new patients.[55] As a result, 79% of the antidepressants prescribed in the United States are prescribed by primary care physicians (PCPs), usually with no input from mental health professionals.[56] These PCPs often lack the very expertise for which the prescription requirement was designed—in essence, creating the barrier without the benefit. Cost also plays a major role in limiting access to SSRI prescriptions. The medications themselves generally are available at low prices. However, in contrast to practitioners in most other specialties, many psychiatrists no longer accept public or private insurance, requiring cash payments in return for service.[57] The percentage of private psychiatrists who have embraced this fee-for-service model is rapidly increasing.[58] These prices are prohibitive for many working and middle class patients. Allowing patients to purchase SSRIs at pharmacies without prescriptions would likely help to surmount both of these existing barriers and increase rates of treatment.

The third barrier identified by Chang et al., comfort, has specific resonance for psychiatric care. Depression remains a highly stigmatized illness among many patients and in many communities.[59] Arnaez and colleagues report that "depression stigma" continues to be "a major impediment to seeking care for those who suffer from the disease."[60] In short, large numbers of individuals with clinical depression are not willing or psychologically able to see a mental health professional. They are reminiscent of the narrator in Donald Barthelme's classic short story, "The Sandman," who writes a letter to a "shrink" and explains in it, "I thought of making a personal visit but the situation then, as I'm sure you understand, would be completely untenable—I would be visiting a psychiatrist."[61] For these individuals, the opportunity to research antidepressants on their own and obtain them through a pharmacy is not an alternative to physician-guided treatment, but rather an alternative to no care at all. They are invisible victims of a policy that requires prescriptions for SSRIs and they suffer significant morbidity and mortality as a result.

Federal law requires a benefit–risk comparison when determining whether a medication should be Rx-only or receive OTC status. Such an approach is reasonable, as the goal of a sensible pharmaceutical policy is to balance respect for patient autonomy with the maximization of patient well-being. The current classification of SSRIs as prescription-only apparently achieves neither objective. On the one hand, consumers are denied the ability to obtain the treatment of their choice on their own terms, supposedly in the name of safety. On the other hand, whether the present policy serves the purpose of protecting consumers is uncertain—and, arguably, unconvincing. As described below, SSRIs do pose some risks. At the same time, barriers to SSRI use also pose significant risks and likely do far more

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damage. That the individuals harmed are invisible is no justification for undervaluing their suffering in the benefit–risk comparison.

Challenges

All medications entail some risks, and SSRIs are no exception. As noted above, the three most serious concerns are suicide, serotonin syndrome, and mania. However, the elevated risk for each of these outcomes specifically secondary to SSRI use remains relatively low, and these sequelae affect only a small percentage of patients. In some cases, the data are still inconclusive. Increased risk of suicide while on SSRIs appears to be limited to adolescents.[62,63] No such effect has been found in older adults.[64] If policymakers are particularly concerned about suicide risk, requiring a prescription for minors or individuals below a certain age, rather than for all individuals, might prove a sensible and least-restrictive option. Moreover, while SSRIs may increase suicides among young adults, no evidence indicates that additional monitoring by a physician has proven protective for adolescents on SSRIs. These deaths may well be the product of impulse and thus an inevitable consequence of outpatient SSRI use in these individuals.

Serotonin syndrome is a life-threatening and dose-dependent condition that remains extremely uncommon. At prescribed SSRI doses, the condition most often occurs in the setting of exposure to multiple serotonergic agents.[65] Since these other agents generally require prescriptions as well, any warning in this regard could satisfactorily be issued at the time these other agents are prescribed. In this way, warnings at the time of an SSRI prescription can be rendered redundant.

Mania is a more frequent, albeit still uncommon, phenomenon correlated with SSRI use for depressive symptoms.[66] Whether the SSRIs cause mania in patients with unipolar depression or merely unmask bipolar disorder remains unclear.[67] In either case, so-called "flipping" into mania is not a benign phenomenon and comes with serious dangers of its own. Yet to what degree additional monitoring for mania by prescribers in the outpatient setting is significantly protective in such cases remains unclear.

Finally, the risk of overdose on SSRIs is as high as with any other medications, possibly higher in light of the patient's underlying risk due to MDD. However, the danger of a fatal or debilitating outcome remains extremely low, and the overdose risk profile for SSRIs compares highly favorably to many current OTC medications. For instance, hepatotoxicity from acetaminophen can occur at any level above the maximum daily dose of 4 g/day.[68] Antidepressants alone are not a common cause of overdose deaths compared to many other prescription drugs. Far more people overdose on antihistamines than on antidepressants.[69] While the risks of suicide and therapeutic misadventure with SSRIs are certainly not insignificant, they are also not more concerning than for many other medications already approved for OTC status.

Conclusion

American medicine, to paraphrase de Tocqueville, too often confounds the familiar with the necessary.[70] That may well be the case with the prescription requirement for SSRIs. While resistance to reclassification of many medications may stem from political pressures and interests, such as physician associations and pharmaceutical manufacturers, that is unlikely the barrier in the case of SSRIs. All of the SSRIs currently on the market are generic and available at low cost, so manufacturers have little incentive to fight against reclassification; if anything, ease of access might increase their sales. Most SSRI prescriptions are not written by psychiatrists, so they are unlikely to seek to protect their "turf" in this area; at the same time, PCPs generally are reluctant to prescribe outside their field of expertise and often would prefer, if possible, to remove themselves from the mental health business entirely. What seems to be keeping SSRIs behind pharmacy counters is a combination of inertia and a systemic bias toward visible victims over invisible ones. A policy intending to protect patients may actually be harming them. At a minimum, calculating the effect of reclassification on morbidity and mortality is necessary to justify continuing the existing policy. Alternatively, as the FDA has done with most other reclassified

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medications, the agency might rely on current evidence to conduct a cost–benefit review that considers the interests of invisible victims. As with such common OTCs that society now takes for granted, such as ibuprofen and loratadine, once a reclassification does occur, patients and psychiatrists alike may wonder how the policy could have ever been any other way.

Competing interest. The authors declare none.

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