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Adverse effects and treatment satisfaction among online users of four antidepressants

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ABSTRACT

Adverse effects (AEs) are an important factor in antidepressant treatment decision-making, though common AE profiles from clinical trial research highlight physical AEs to the neglect of emotional and behavioral AEs. First-hand accounts of antidepressant users on the Internet can supplement AE profiles with information gained from real-world treatment experiences. We examined online user reviews of two older (escitalopram; duloxetine) and two newer (vilazodone; vortioxetine) antidepressants for differences in their AE profiles and determined which categories of AEs were associated with users' satisfaction. A codebook of 60 physical, emotional, and behavioral AEs was used for line-by-line coding of effects reported among 3243 user reviews from three popular health websites. Emotional and behavioral effects were commonly reported (41%), followed by sleep (31.9%) and gastrointestinal (25.0%) effects. Specific AEs statistically significantly varied across drugs, creating potentially meaningful differences in AE profiles. Users of newer drugs more often reported emotional instability, while users of older drugs reported more emotional blunting. Emotional and behavioral AEs demonstrated moderate to substantial relationships with users' satisfaction, whereas gastrointestinal, metabolic, or sexual AEs were minimally related. More specific and systematic assessment of a broader range of AEs is needed in both research and practice.

1. Introduction

An estimated 13% of American adults currently take an antidepressant medication, double the number of adult users compared to the turn of the century (Kantor et al., 2015). While about a dozen SSRI and SNRI antidepressant brands exist on the market and new multi-modal antidepressants have more recently been released, clinical trial research demonstrates generally comparable efficacy and adverse effect (AE) profiles across most of these drugs (Gartlehner et al., 2011; Jakobsen et al., 2017; Richelson, 2013). Common AEs associated with antidepressant treatment according to clinical studies are nausea, vomiting, diarrhea, dry mouth, sweating, headache, dizziness, anxiety, tremor, insomnia, sexual dysfunction, and weight gain (Crawford et al., 2014; Gartlehner et al., 2011). In the largest survey to date of antidepressant users (n = 1829), Read et al. (2014) further found high rates of emotional and interpersonal AEs, including feeling emotionally numb (60.4%), feeling not like myself (52.4%), reduced positive feelings (41.7%), and caring less about others (38.8%). Emotional AEs and the phenomenon of SSRI-induced indifference have received scant attention in clinical studies and are not commonly listed in the literature as part of antidepressants' known or expected AE profiles (Price et al., 2009; Sansone and Sansone, 2010). As some of these same emotional effects might be considered desirable or effective to some degree in the context of relieving depression or anxiety, their categorization as therapeutic or adverse is not always easily distinguishable.

Neglect of emotional and behavioral AEs might also be explained by the failure of clinical studies to systematically assess AEs as part of standard trial methodology (Hughes et al., 2016). In randomized controlled trials used to obtain FDA-approval for a new psychiatric drug, AEs are identified primarily using spontaneous self-report or open-ended questioning (Hughes and Cohen, 2010; Hughes et al., 2016). These unstructured methods are known to reduce the estimated prevalence of AEs and limit the identification of AEs to those that are most easily detectable, such as gastrointestinal and nervous system effects. Despite limitations, most of what is known about antidepressants' AEs at the time of marketing is generated from these studies.

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Post-marketing effectiveness studies provide the opportunity to learn more about a drug's effects on typical users in real-world clinical contexts. The federally funded Sequenced Treatment Alternatives to Relieve Depression study, for example, systematically monitored the presence and severity of AEs using the PRISE checklist (Rush et al., 2004). The PRISE, however, only assesses physical effects on eight body systems, listing a few emotional or behavioral effects, including anxiety, poor concentration, and restlessness, within an "other" category. While other instruments have been developed to systematically assess for emotional and behavioral AEs, none has been well tested or widely adopted (Sansone and Sansone, 2010). Greater attention to identifying and monitoring AEs is important because users' experience of AEs, both physical and emotional/behavioral, plays a major role in treatment decision-making (Bolling and Kohlenberg, 2004). Further, in light of antidepressants' increasingly questionable benefits, consideration of drug harms and perceived quality of life are positioned to take more prominent roles in practice and research (Jakobsen et al., 2017). While prior research has described rather similar AE profiles among second-generation antidepressants (Gartlehner et al., 2011), without proper assessment of a range of AEs, it remains unclear how either measured or unmeasured effects might vary between antidepressants or impact users' satisfaction.

The problem of poor AE assessment and reporting in published drug studies is long recognized (Ioannidis and Lau, 2001; Jacobs and Cohen, 1999), though little progress has been made towards more systematic assessment of a range of physical, emotional, and behavioral AEs (Hughes et al., 2016; Ioannidis, 2009). Information on AEs for new antidepressants on the market thus remains limited and narrowly understood until large numbers of real-world users and clinicians report their experiences. User drug reviews on the Internet offer a unique opportunity for rapid feedback about how new drugs to market are being experienced, with the potential to provide additional clues on important AEs to monitor in clinical practice. Few other opportunities exist to gather first-hand reports from large numbers of users, and prior studies have found online users' accounts useful for complementing more formal sources of drug information (Goldsmith and Moncrieff, 2011; Hughes and Cohen, 2011; Moncrieff et al., 2009). For example, an analysis of online antidepressant and antipsychotic user reviews found that while drug information constructed by health professionals provided concise listings of physical drug effects, users' descriptions provided richer contextual information for how the same effects were experienced in daily life (Hughes and Cohen, 2011). A content analysis of Internet postings from one website confirmed the presence of both sedating and activating psychoactive effects in users' descriptions of antidepressants. While patient-reported experiences of emotional and behavioral AEs have been well-documented in prior research (Bolling and Kohlenberg, 2004; Goldsmith and Moncrieff, 2011; Read et al., 2014), the relative impact of different types of AEs on patients' satisfaction with their antidepressant remains unknown. The purpose of the present study was to 1) examine online user reviews of two well-established antidepressants and two newer antidepressants for differences in their AE profiles, and 2) determine which categories of AEs are associated with users' overall satisfaction with their antidepressant.

2. Methods

2.1. Sample and data collection

Four drugs commonly used in the treatment of depression were purposively selected according to their FDA approval dates for a major depressive disorder indication. Escitalopram, a SSRI approved in 2002, and duloxetine, a SNRI approved in 2004, were selected as top-prescribed antidepressant agents with lengthy histories on the drug market and ample clinical testing for efficacy and safety. Both drugs have consistently topped the antidepressant market in number of prescriptions and sales revenues. Two additional drugs, vilazodone (approved in 2011) and vortioxetine (approved in 2013) were selected for their status as newer agents with fewer completed clinical studies and less post-marketing experience to inform clinicians and users on the full range of AEs. Vilazodone was the third most prescribed antidepressant in 2013–2014, while vortioxetine has demonstrated a slower than expected uptake in the U.S. market, though still reaching nearly $60 million in U.S. revenues in 2015 (Lundbeck Pharmaceuticals, 2016a). Both drugs are marketed as novel multi-modal antidepressant agents with effects on multiple 5-HT receptors, and promoted as a better first-line strategy prior to antidepressant augmentation with other drugs (Richelson, 2013). Tolerability profiles of these new multi-modal agents are reported to be similar to existing SSRIs, including nausea, diarrhea, dizziness, headache, dry mouth, and insomnia (Richelson, 2013). Published reviews further suggest minimal sexual dysfunction and weight gain relative to existing SSRIs (D'Agostino et al., 2015; Wang et al., 2013). Given that the limited data available on these new drugs is funded and controlled by the drugs' manufacturers, it is likely that their full AE profile remains unexplored and that meaningful differences compared to older drugs might exist. The analysis of Internet postings of users' reviews of these drugs might provide important additional information about harms and AEs yet to emerge in official channels of testing and surveillance. It was hypothesized for all four drugs that a greater range of emotional and behavioral AEs would emerge from users' online postings than appears in published clinical trials, however no hypothesis was made in advance regarding specific potential differences in types of AEs reported between antidepressants.

Online user reviews for escitalopram, duloxetine, vilazodone, and vortioxetine were collected from three websites popular for their accumulation of first-hand user drug ratings and reviews: the professional health portals WebMD and EverydayHealth, and the patient-generated website AskAPatient. In September 2015, all user reviews on the four drugs from three websites were copied and pasted into Microsoft Excel. Non-mood related reasons for use (e.g., duloxetine for fibromyalgia) were excluded from the analysis. Duplicate, empty, or incoherent entries were also excluded. Due to a large number of reviews on escitalopram for mood-related conditions, a 50% systematic random sample was collected with every other review chosen. The final sample consisted of 3243 user reviews on the four drugs: escitalopram, n = 2359 (72.7%); vilazodone, n = 394 (12.1%); duloxetine, n = 305 (9.4%); vortioxetine, n = 185 (5.7%). Each review consisted of a 1–5 star rating of the drug, the indication or condition the drug was being used for, an open text entry for comments about the drug experience, sex and age range of the user, and duration of use of the drug being reviewed. The Colorado State University Research Integrity and Compliance Review Office approved this study.

2.2. Coding

All 3243 user reviews were imported from Microsoft Excel into QDA Miner 4.1.22 software for coding (Peladeau, 2013). A codebook of 60 possible AEs was developed based on multiple sources. First, AEs commonly appearing in published clinical trials of antidepressants were listed according to preferred terms based on the most commonly used coding system, the Medical Dictionary for Regulatory Activities (MedDRA) (see Le Noury et al., 2015). Specific AEs were categorized within MedDRA system organ class (SOC) groupings, which include cardiovascular, gastrointestinal, psychiatric, nervous system, metabolic, musculoskeletal, and skin disorders. Additional emotional and behavioral effects, such as emotional numbing, were added based on a previously published survey of antidepressant users (Read et al., 2014). Once an initial list of AEs was constructed from these published sources, two coders (i.e., the first author and a trained Masters-level research assistant) independently completed two rounds of practice coding on 45 and 60, respectively, randomly selected user reviews. Three additional effects emerged from practice coding, including brain zaps, sleep