Review Article

Clinical perspectives on the influence of drug formulation on patient tolerability and use of commonly prescribed antidepressants in major depressive disorder

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ABSTRACT

The purpose of this review is to summarize the formulation options for currently available antidepressants, and discuss examples of the influence that formulation may have on the pharmacologic and clinical profiles of the medications. A review of current literature suggests that differences in drug-delivery technologies can lead to variations in the pharmacokinetic and pharmacodynamic profiles of generic and branded drugs, despite generic drugs being required to meet bioequivalence standards compared with their branded counterparts. These differences may influence the effectiveness and tolerability of treatment. Recent reports have highlighted the need for individualized treatment regimens and careful assessment of tolerability and efficacy when switching patients from brand to generic formulations. There is a growing body of evidence indicating that differences in formulation can substantially impact drug pharmacokinetics and pharmacodynamics, which in turn, can affect drug effects. The clinical impact of these differences remains unclear. Further research is needed to clarify the influence of antidepressant formulations on treatment adherence, patient preference, and quality of life, and how this impacts clinical practice with regard to brand versus generic treatment selection.

INTRODUCTION

Major depressive disorder (MDD) is characterized by persistently low mood, disturbed neurovegetative functions, and abnormalities in cognition and psychomotor activity.[1] People with MDD often experience a loss of interest in previously enjoyable activities[2] and feelings of worthlessness and inappropriate guilt.[1]

According to the DSM-5 criteria published in 2013, a person is considered to have MDD if he/she has at least five symptoms nearly every day for 2 weeks, including depressed mood or increased irritability, decreased interest or pleasure, significant weight or appetite change, change in sleep patterns, change in activity, fatigue, feelings of guilt or worthlessness, issues with concentration, and suicidal thoughts.[3] Additionally, at least one of the symptoms should be depressed mood or loss of interest, which is a change from normal baseline and results in clinically significant distress or impairment in function socially or with other activities, and is not associated with substance abuse or another medical condition.[3]

Estimates of the prevalence of MDD vary widely, but it is thought that between 4% and 10% of the world's population will likely experience a major depressive episode sometime during their lifetime.[4] MDD is more prevalent in adults aged between 18 and 59 years, women, and those living in or near poverty.[5] Risk factors associated with MDD include

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being divorced, separated, or widowed; trauma in childhood, illness, and significant life events, such as divorce or death of a close relative.[6]

Some individuals with MDD are at high risk for suicide.[7] In a 5-year prospective study of patients with MDD, 14.5% attempted suicide at least once.[8] It has been estimated that the risk of suicide-associated death in individuals with MDD is as much as 20-fold higher than the general population.[9]

There are a number of pharmacologic therapies for the treatment of MDD that are available in a variety of drug formulations. Furthermore, there is a growing body of evidence indicating that differences in formulation can substantially impact pharmacokinetics (PK), which in turn, can affect treatment efficacy and drug tolerability. This is evident when comparing generics to branded agents, where different formulations have been shown to have a significant impact on the pharmacologic and clinical profile of various antidepressants.[10,11] The purpose of this review is to discuss these drug formulation options, their influence on the pharmacologic profiles of commonly prescribed antidepressants, and the subsequent effect these differences may have in the clinical setting.

Current treatment approaches and available pharmacologic treatment options

The mainstay of treatment for MDD is pharmacologic intervention with antidepressants.[2] The selection of pharmacologic therapy is dependent upon multiple factors including patient choice, side effects, tolerance of the individual patient, pharmacologic properties, and patient prior experience with antidepressants.[12]

The antidepressants currently prescribed for the treatment of MDD comprise eight main classes: The monoamine oxidase inhibitors (MAOIs), norepinephrine-dopamine reuptake inhibitors (NDRIs), serotonin modulators (SM), noradrenergic and specific serotonergic antidepressants (NaSSAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and tetracyclic antidepressants (TeCAs). Examples of currently used antidepressants are provided in Table 1.

MAOIs

MAOIs exert their pharmacologic actions by inhibiting the enzyme monoamine oxidase, thereby increasing levels of monoamine neurotransmitters and increasing synaptic transmission. Although MAOIs were the

Table 1: Examples of antidepressants currently used for the treatment of MDD

Generic name	Classification	Available formulations	Available dosage forms	Technology	Generics available
Bupropion[14]	NDRI	Immediate-release tablets	75 or 100 mg	*	Yes
		Sustained-release (SR) tablets	100, 150, or 200 mg	Film coated	
		Extended-release (XL) tablets	150 mg	Insoluble shell	
Citalopram[26]	SSRI	Tablets	10, 20, or 40 mg	*	Yes
		Oral solution	2 mg/ml	*	
Desvenlafaxine[68]	SNRI	Tablets	50, 100 mg	*	Yes
		Extended release tablets	50, 100 mg	Film coated	
Duloxetine[69]	SNRI	Delayed-release capsules	20, 30, or 60 mg	Enteric coating	No
Escitalopram[26]	SSRI	Tablets	5, 10, or 20 mg	Film coated	No
		Oral solution	1 mg/ml	*	
Fluoxetine[36]	SSRI	Pulvule®	10, 20, or 40 mg	Patented technology	Yes
		Weekly capsule	90 mg	Enteric coating	
		Oral solution	4 mg/ml[19]	*	
Mirtazapine[17,18]	NaSSA	Tablets	15, 30, or 45 mg	Film coated	Yes
		Orally disintegrating tablets	15, 30, 45 mg	*	
Paroxetine[70,71]	SSRI	Tablets	10, 20, 30, 40 mg	*	Yes
		Oral suspension	10 mg/5 ml	*	
		Controlled-release tablets	12.5, 25, 37.5 mg	Enteric coating	
Selegiline[72]	MAOI	Transdermal system	≤12 mg/24 h	Matrix transdermal patch	
Trazodone[15]	SM	Tablets	50, 100, 150, or 300 mg	*	Yes
Venlafaxine[43]	SNRI	Tablets	25, 37.5, 50, 75, or 100 mg	*	Yes
		Extended-release (XR) capsules	37.5, 75, or 150 mg	Osmodex® technology	

MAOI=Monoamine oxidase inhibitor, MDD=Major depressive disorder, NaSSA=Noradrenergic and specific serotonergic antidepressant, NDRI=Norepinephrine-dopamine reuptake inhibitor, SM=Serotonin modulator, SNRI=Serotonin and norepinephrine reuptake inhibitor, SSRI=Selective serotonin reuptake inhibitor. Pulvule® is a registered trademark of Eli Lilly, Indianapolis, IN, USA. Osmodex® is a registered trademark of Osmotica Pharmaceutical Corp, Wilmington, NC, USA. *Conventional dispersible oral tablet or oral solution technology

first prescribed antidepressant therapy and have been available for more than 50 years, they are presently prescribed as a last-line treatment due to the potential for serious food–drug and drug–drug interactions.[13]

NDRIs

Bupropion is currently the only NDRI approved by the US Food and Drug Administration (FDA) for the treatment of MDD. Bupropion inhibits the neuronal uptake of norepinephrine and dopamine, demonstrating a different mechanism of action to the SSRIs, SNRIs, and MAOIs.[14]

SMs

The SMs are antagonists of serotonin receptors–specifically, the $5HT_2$ receptors. However, these compounds have additional properties and it is unclear whether their mechanism of action is directly associated with serotonin receptor antagonism.[15,16]

NaSSAs

The NaSSAs, such as mirtazapine, enhance central noradrenergic, and serotonergic activity.[17,18] They are believed to work through their antagonistic activity of central presynaptic α_2 adrenergic inhibitory autoreceptors and heteroreceptors.

SNRIs and SSRIs

SSRIs act by inhibiting the reuptake of serotonin into the presynaptic neuron, thereby increasing the level of serotonin in the synaptic cleft and increasing neurotransmission. SNRIs inhibit the reuptake of both serotonin and norepinephrine.[19]

TCAs and TeCAs

The TCAs were first developed in the 1950s for the treatment of depression, but they are now used less frequently than SSRIs and SNRIs, which have demonstrated more favorable safety and tolerability profiles.[19-21] TeCAs are closely related to the TCA class of antidepressants. Guidelines currently recommend that TCAs should be reserved for use after first-line treatment with another antidepressant has failed.[22]

Treatment choice

The first-line pharmacologic treatment choice is generally considered to be an SSRI[22] and as such they are the most commonly prescribed class of antidepressant. One prospective observational study across 12 European countries found that 63.3% of patients with MDD were prescribed an SSRI.[23] Despite this, antidepressant effectiveness is generally considered comparable among and within classes of medication.[12] A number of recent literature reviews compare the efficacy, safety, and tolerability of the currently available second-generation antidepressants, such as the SNRI and SSRIs.[24-28] In particular, Gartlehner *et al*. reported that clinical response and remission rates when treating acute-phase MDD are comparable among antidepressants.[26] Adverse event profiles were broadly similar, although differences in specific adverse events were identified.[26] Similar findings were also reported by Mackay *et al*., who investigated the incidence of adverse events in patients treated with one of six commonly prescribed antidepressants in the United Kingdom.[28] The most common adverse events with all six antidepressants were nausea and vomiting, with this occurring more frequently in patients taking the SNRI venlafaxine than in patients taking the other drugs investigated.[26,28]

Formulations and technology

In addition to the wide variety of antidepressants, a number of antidepressants are available in different formulations. Particular formulations may have variations in bioavailability and PK that suit individual patient needs and symptoms, and these formulations may also be employed to overcome pharmacologic barriers associated with some treatments. In general, antidepressants that can be administered as once-daily are preferred.

Controlled-release formulations are favored over immediate-release (IR) formulations due to the decreased variability in plasma levels between doses.[29] Controlled-release formulations can allow for a decrease in the frequency of dosing compared with IR formulations, such as conventional dispersible oral tablets, while maintaining drug concentrations within the therapeutic range.[29] In addition, controlled-release formulations may have the potential to improve tolerability, thus reducing the frequency or severity of adverse events and improving treatment adherence.[30,31]

There are a number of drug-delivery systems for controlled-release formulations that have been specifically designed to offer steady drug delivery over extended time periods.[32] Some examples of drug-delivery systems are illustrated in Figure 1. One such oral drug-delivery system is extended-release (ER) tablets that contain the active component embedded in a matrix of insoluble substances such as acrylics, allowing the drug to dissolve over time and be steadily released. ER capsules are also available that contain microbeads, or microspheres, which delay dissolution compared with conventional capsules that contain the active ingredient in powdered form.

Another oral drug delivery system involves the process of micro-encapsulation whereby an inert

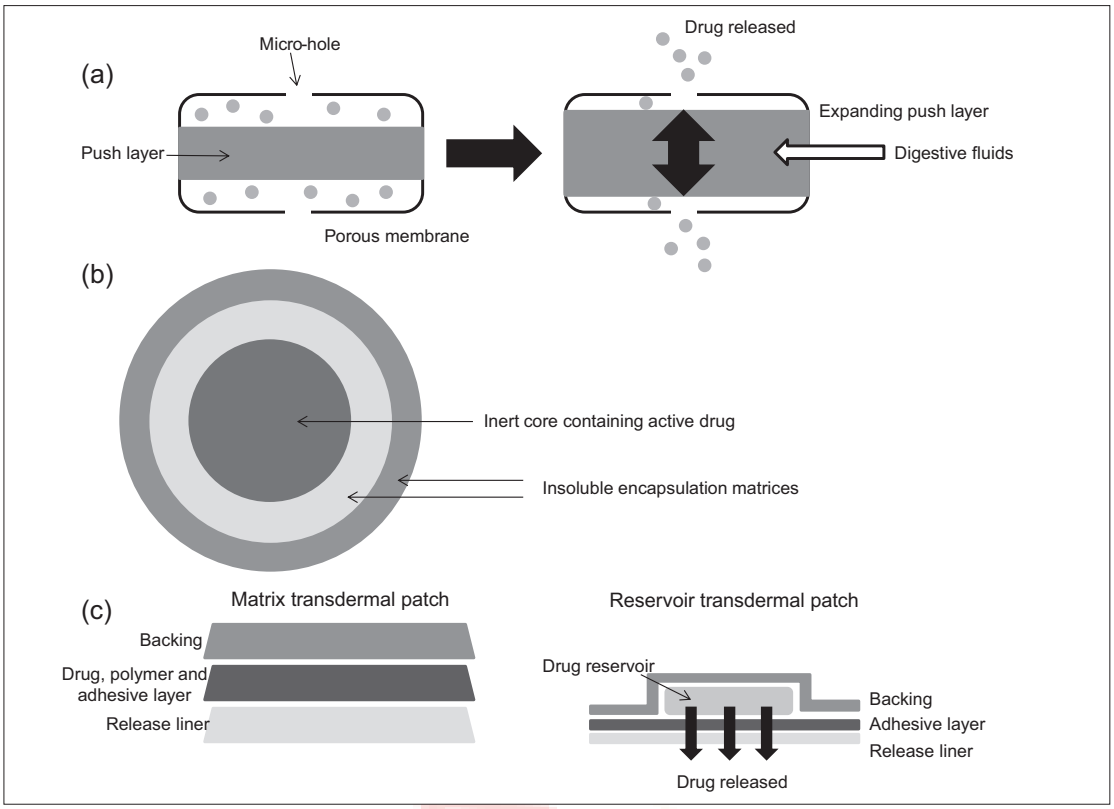

Figure 1: Drug-delivery systems. (a) Microhole osmotic delivery, (b) Micro-encapsulation, (c) Transdermal patch delivery

core containing the active ingredient is layered with various insoluble matrices, enabling more consistent, controlled, and replicable dissolution rates. The active ingredient can be released from the microcapsule by various methods, depending on the coating employed. These include: (a) diffusion, where the dissolution fluid is able to penetrate the coating and dissolve the core containing the active drug, releasing it through channels or pores; (b) dissolution, where the solubility and thickness of the coating controls the rate at which the coat dissolves and the drug is released; and (c) erosion, where the coating is eroded over time due to pH and enzymatic hydrolysis, allowing the drug to be released.[33] Other micro-encapsulation systems include osmotic, polymer-based tablets with a micro-hole on one side and a porous membrane on the other. The coating behaves as a semi-permeable membrane that allows digestive fluids to perfuse through, creating an osmotic pressure gradient that pushes the drug out.[33]

In addition to various tablet-based technologies, transdermal patches employ a variety of reservoir or gel-matrix-based delivery technologies to ensure smooth and consistent drug delivery over time. Transdermal patches allow the delivery of molecules with certain properties (e.g., small, lipophilic) to be absorbed directly into the bloodstream through the skin. Reservoir transdermal patches contain the active ingredient within a raised compartment; the drug is allowed to diffuse through a polymer membrane that controls the rate of release. Matrix patches contain the active component, adhesive, and polymer membrane within one layer and as a result tend to be smaller and thinner than reservoir patches.[34]

Transdermal patches can provide benefits over some oral therapies by permitting once-daily administration, bypassing first-pass gastrointestinal and hepatic metabolism and thus reducing the risk of drug–drug interactions.[34] However, disadvantages of transdermal patches include PK issues because of the low intrinsic permeability of the skin, cutaneous reactions, and the potential for increased drug exposure and toxicity due to misuse and damage to the patch.[34]

Pharmacokinetics, pharmacodynamics, and potential benefits of extended-release versus sustained- and immediate-release formulations

Oral administration of a drug typically results in rapid peak plasma concentrations (C_{max}) followed by a decline until plasma concentrations are at their lowest (C_{min}). The optimal therapeutic window falls within these ranges.[35] Different formulations of a drug can provide equivalent bioavailability in terms of drug exposure over time (area under the curve, AUC), but with differing PK profiles. Adverse effects of

pharmacologic treatments are often associated with high C_{max} and a short time to reach this maximum (t_{max}). As mentioned previously, controlled-release formulations of compounds with short half-lives reduce the C_{max} and increase the t_{max}, potentially improving tolerability while retaining efficacy. The reduced side effects that may be associated with controlled-release formulations may also help to improve adherence to treatment, helping to optimize the effectiveness of treatment in the real-world setting.[31]

Comparison of antidepressant formulations

Second-generation antidepressants are available in a range of formulations [Table 1]. These different formulations, with their potentially dissimilar PK properties, can impact patient outcomes, tolerability, and adherence to treatment. The following examples of second-generation antidepressants have more than one available formulation. These examples provide evidence that differences in formulation or delivery mechanisms may affect efficacy or tolerability.

Fluoxetine weekly versus daily formulations

Fluoxetine (an SSRI) weekly capsules consist of enteric-coated pellets that are resistant to dissolution until they reach an area of the gastrointestinal tract where the pH is in excess of 5.5.[36] Weekly dosing reduces the patient's medication burden and may help to improve adherence over daily dosing.[37,38] The efficacy and safety of daily and weekly formulations of fluoxetine have been compared in a number of studies.[39-41] The daily Pulvule® (a proprietary capsule containing the active compound in powdered form; Eli Lilly, Indianapolis, IN, USA) and weekly fluoxetine capsules are bioequivalent,[36] and weekly fluoxetine has been shown to have a similar tolerability profile to the daily, IR formulation.[42] However, the plasma concentration fluctuations are more pronounced with weekly than with daily dosing, with differences between the trough and peak values being 24% for daily dosing and 164% for weekly dosing.[36] Despite this, the C_{max} values are similar for daily and weekly administration.[36]

Despite the similar tolerability profiles between the daily and weekly administration of fluoxetine, there may be differences in treatment adherence among patients taking the two regimens.[37,38] In a study published by Claxton *et al.*, 109 subjects who previously were taking fluoxetine 20 mg once daily for 4 weeks were randomly assigned to recieve either fluoxetine 20 mg once daily (53 patients) or fluoxetine 90 mg once weekly (56 patients) in a 12-week, open-label continuation phase to study compliance.[37] There was no significant change in mean adherence in patients who switched from taking fluoxetine 20 mg once daily to fluoxetine 90 mg once weekly (85.4-87.5% adherence, $P = 0.541$), while a significant decrease in adherence was observed in those patients who remained on the fluoxetine 20 mg once-daily regimen (87.3-79.4% compliance, $P < 0.001$).[37] Not surprisingly, having to take a pill less frequently improves treatment adherence.

Venlafaxine: Extended-release versus immediate-release formulations

The SNRI venlafaxine is available in ER and IR formulations. Once-daily administration of venlafaxine ER results in lower C_{max} and longer t_{max} than twice-daily administration of venlafaxine IR (C_{max}: 150 ng/mL vs. 225 ng/mL, t_{max}: 5.5 vs. 2 hours).[43] In a double-blind, randomized, placebo-controlled trial, venlafaxine ER demonstrated superior efficacy to venlafaxine IR ($P < 0.05$).[44] A risk–benefit analysis of a double-blind, placebo-controlled study of patients with MDD found that venlafaxine ER demonstrated a superior benefit–risk ratio over venlafaxine IR, with significant differences shown for nausea ($P = 0.013$) and dizziness ($P = 0.029$).[45]

In addition, a report by Haeusler[46] investigated how a change from venlafaxine ER capsules to venlafaxine ER tablets could potentially impact medication burden, costs, and treatment adherence. Tablets allowed for a maximum dose to be administered with a single item as opposed to the three needed with ER capsules. Tablets also have a lower cost. For example, a 225 mg tablet costs $6.06 while an equivalent dosage with a capsule formulation is priced from $7.75 to $11.12.[46] The authors concluded that venlafaxine ER tablets may reduce costs, reduce "pill burden," and improve adherence versus capsules.[46]

Selegiline: Transdermal versus oral administration

A transdermal formulation (matrix patch) of the MAOI selegiline is approved by the US FDA for the treatment of MDD. Although efficacious,[47,48] there is extensive first-pass metabolism associated with oral selegiline in the doses required for efficacy, and antidepressant-related dietary restrictions are necessary.[49] In the treatment of MDD, a MAOI should inhibit brain MAOI-A and MAOI-B, but not gastrointestinal MAOI-A; oral selegiline does not demonstrate specificity at the doses required for antidepressant efficacy.[49] A randomized, double-blind, placebo-controlled trial was conducted to assess the safety and efficacy of the selegiline transdermal system (20 mg patch applied once daily) in patients with MDD.[50] The results of this study

showed that selegiline transdermal system was more effective than placebo.[50] Furthermore, transdermal delivery resulted in minimal interaction with dietary tyramine, reduced exposure to drug metabolites, and sustained exposure to therapeutic levels of the drug.[50] This was subsequently confirmed in an 2005 FDA report, which showed that patients receiving transdermal doses of up to 40 mg of selegiline daily for 10 days had clinically acceptable sensitivity to tyramine. Nevertheless, because of the limited clinical experience, the FDA recommends dietary restrictions for patients prescribed the 30 and 40 mg doses.[51]

Bupropion: Extended-release versus immediate-release formulations

The efficacy of the IR formulation of bupropion has been demonstrated in a number of clinical trials.[52-55] Further trials have demonstrated the efficacy of bupropion sustained release (SR)[56] and bupropion XL (ER) in patients with MDD[57] and demonstrated that bupropion XL is bioequivalent to the SR and IR formulations.[14] The bioequivalence of bupropion IR, SR, and XL have been extensively reviewed in the literature. All three formulations have similar bioavailability (AUC) and C_{max}, although this is slightly reduced with the XL dosing schedule compared with the IR and SR formulations.[58] The t_{max} is delayed with the XL and SR formulations compared with that of the IR formulation (approximately 5, 3, and 1.5 hours, respectively).[58,59] These data indicate a potentially improved tolerability profile with XL and SR formulations compared with IR formulations while maintaining drug exposure and clinical efficacy.[59] The potentially improved tolerability is shown by the lower incidence of seizures at doses of 300 mg/day with the SR formulation (0.1%) compared with doses of 300-450 mg/day for the IR formulation (0.4%).[58]

Although drugs may be deemed biologically equivalent, differences in formulation can impact PK profiles.[59] These differences can affect treatment adherence, adverse events, and even treatment efficacy.[46,50] Comparisons of daily and weekly formulations of fluoxetine found the formulations to be bioequivalent[36] with similar tolerability profiles,[39] despite the increased plasma fluctuations observed with the weekly capsule. ER formulations can influence tolerability by reducing plasma concentration fluctuations and can provide improved convenience for patients in terms of reducing "pill burden" and frequency of dosing. Furthermore, different delivery mechanisms, such as transdermal patches, can provide efficacious doses that are otherwise restricted with oral therapies.[34] Given the similarities in efficacy and tolerability among current classes of pharmacologic therapies for MDD, the importance of drug-delivery technologies on patient outcomes cannot be underestimated.

Bioequivalence of branded versus generic formulations

To be approved by the FDA, generic drugs must contain the same active ingredients as the brand name drug; be identical in strength, dosage form, and route of administration; have the same indications for use; be bioequivalent; meet the same batch requirements for identity, strength, purity, and quality; and be manufactured under the same good manufacturing practices required for brand name products. Bioequivalence is defined by the FDA as "*the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.*"[60]

Small differences in C_{max} and AUC are permitted between brand and generic drugs and are not considered clinically relevant. The FDA guidance advises that two drugs are bioequivalent in terms of their bioavailability if the 90% confidence interval (CI) values of the mean C_{max} and AUC are between 80% and 125%.[60]

Comparison of branded and generic formulations

There are a number of generic antidepressants available. While these provide the same active compound as their branded counterparts, the delivery technology–and therefore, the PK, PD, and potentially the effectiveness of treatment–may differ considerably. How much this may impact clinical efficacy is not clear. The following are examples of generic formulations of antidepressants where questions have been raised regarding their bioequivalence with corresponding brand formulations.

Bupropion XL

The first generic version of bupropion was approved by the FDA in 2006. In 2008, an article was published describing patients who reported worsening side effects and a relapse of depressive symptoms after switching from branded to generic ER bupropion, primarily at the 300 mg dose.[61] The FDA began to investigate these reports and reexamined the available data on generic bupropion. There have since been a number of reports to the FDA of undesirable effects in patients who were switched from branded to generic

bupropion XL.[62] A study found that generic bupropion XL was released at a different rate compared with the branded drug. It was suggested that the time-release technology of the generic drug might be different from that of the branded product and could explain the variation in t_{max} observed in the study.[63]

The FDA subsequently determined that there was no significant difference in the rate and extent of bupropion absorption with a 150 mg dose of brand bupropion XL or generic bupropion XL.[62] The average generic bupropion XL C_{max} was 89% (90% CI 80.3-98.2%) of branded bupropion XL, and the average generic bupropion XL AUC was 98% (90% CI 91.9-104.4%) of branded bupropion XL in the same group of healthy volunteers under fasting conditions.[62] Similarly, hydroxybupropion, the major active metabolite, was found to fall within the C_{max} and AUC bioequivalence limits. In contrast, t_{max} is not required to be within specific limits for FDA approval. The generic bupropion XL t_{max} was 2-3 hours versus 5-6 hours for brand named bupropion XL. These differences were not considered to be clinically significant.[62] Furthermore, the FDA thought that these results could be extrapolated to the 300 mg dose.[62]

However, public interest in the bioequivalence of branded and generic versions of 300 mg ER bupropion led the FDA to revisit this issue and to perform studies in 24 healthy adult volunteers comparing the 300 mg dose of generic Budeprion XL to branded bupropion XL.[10,11] In findings reported in August 2012, the FDA determined that Budeprion XL 300 mg tablets did not release bupropion into the blood at the same rate and extent as the branded bupropion XL 300 mg tablet. Specifically, Budeprion XL 300 mg absorption (represented by AUC) was 86% (90% CI 77-96%) of the branded bupropion XL 300 mg.[11] Furthermore, the C_{max} of Budeprion XL 300 mg was 75% (90% CI 65-87%) of that obtained with branded bupropion XL 300 mg.[11] As a consequence, Budeprion XL 300 mg was withdrawn from the market in October 2012 at the request of the FDA.[10,11]

Venlafaxine

Generic venlafaxine was approved by the FDA in 2010 for the treatment of MDD. A randomized crossover study compared the PK profiles of brand versus generic venlafaxine and citalopram in healthy male volunteers.[64] The C_{max} for generic venlafaxine was higher than that observed for branded venlafaxine and fell outside of the generally accepted 80-125% limits for bioequivalence. There were three times more side effects reported when participants were taking generic venlafaxine than when taking branded venlafaxine XR.[64] The authors postulated that the differences were related to the different controlled-release mechanisms used (three different sized spheres within the capsule for branded venlafaxine versus all one sized sphere within the capsule for generic venlafaxine). The findings of Chenu *et al*. suggest that generic venlafaxine may not be bioequivalent to the branded product, and that these differences may impact tolerability of treatment;[64] however, further clinical evidence is required to confirm this.

Other recent reviews of brand versus generic formulations

A recent literature review relating to switching from brand to generic psychotropic medications found numerous reports of loss of efficacy and/or increased adverse events when patients were switched from branded psychotropic medications to generics.[65,66] Patients who had negative clinical outcomes when switched to generic drugs improved when they were switched back to their original medication.[66] Recent reports have highlighted the need for individualized treatment regimens and a careful assessment of tolerability and efficacy when switching from brand to generic drug formulations.[65]

Healthcare cost implications with brand versus generic formulations

One of the major considerations when comparing brand versus generic antidepressants is relative cost. One recent study assessed disease-specific and total healthcare costs in the first 6 months of treatment following initiation of brand versus generic antidepressant medication (SSRI and SNRI therapies).[67] It was reported that there were significant differences in associated cost; the adjusted average 6-month healthcare costs were $3660 (95% CI $3538-3787) for patients who received generic drugs versus $4587 (95% CI $4422-4757) for those who initiated treatment on branded drugs ($P < 0.001$).[67] Furthermore, the adjusted average 6-month SSRI/SNRI costs were $174 (95% CI $169-180) versus $309 (95% CI $300-319) for generic and branded drugs, respectively ($P < 0.001$).[67] It was concluded that generic SSRI or SNRI therapies are associated with reduced total healthcare and drug costs.[67]

CONCLUSION

Current classes of MDD treatment are broadly similar with regard to efficacy, tolerability, and adherence.[12] There are differences among formulations that can substantially impact the PK and PD of therapy and

which, in turn, can impact the effectiveness of treatment by influencing tolerability, efficacy, and adherence. However, efficacy data for different formulations appear generally comparable, and advantages may be most pronounced in the area of medication-taking burden.

The majority of the published literature appears to suggest that there may be differences in drug delivery or availability between generic and branded antidepressant drugs. In some instances these differences may be also associated with variations in clinical response. This was recently shown in the comparison between branded bupropion XL 300 mg and generic Budeprion XL 300 mg.[10,11] There is also a pronounced difference in cost between generic and branded antidepressant medication. Decisions to use generic versus branded formulations should therefore consider tolerability and efficacy in the individual patient, as well as overall costs. While costs are lower with generic antidepressant medications some patients can have depressive relapse when switched from name brands to generic brands. Therefore further research is needed to assess the influence of drug formulations on both short- and long-term efficacy, safety, and quality of life. In addition, the influence of socioeconomic factors on patient medication choice and adherence needs to be better understood. A more complete awareness of these factors will further aid in the decision process for the treatment of MDD.

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