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Expert Opinion

Paroxetine mesylate: comparable to paroxetine hydrochloride?

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Importance of the field: Currently available small case reports clearly propose that existing regulatory procedures to approve generic versions only require essential bioequivalence, have limitations and fail to meet stricter scientific and clinical demands.

Areas covered in this review: Data indicate that paroxetine mesylate has some potential differences in bio- and clinical equivalence compared with paroxetine hydrochloride, although it has not been fully and sufficiently investigated in well-designed clinical trials. Data available now regarding safety, tolerability, efficacy and practical issues dealing with debates between generic and brand-name products paroxetine mesylate and paroxetine hydrochloride are presented in the review.

What the reader will gain: Preclinical and clinical data are reviewed, and clinical issues relating to use of generic version versus original product are comprehensively discussed; tips for the clinician in clinical practice are also provided.

Take home message: Potential differences in efficacy and safety but also reduction in the use of health care and in pharmacy cost should be considered when choosing the generic version or the original product based on the clear benefit–risk ratio in patients.

Keywords: brand-name product, generic, paroxetine hydrochloride, paroxetine mesylate, safety, tolerability

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1. Introduction

It is well known that major depressive disorder (MDD) affects an estimated 121 million people worldwide; and in 2008, the antidepressant drug market reached sales of almost $11 billion [1]. Although there are several new antidepressant candidates in the industry pipeline, more than $5 billion worth of current branded drugs will be off-patent by 2014, enabling the entrance of cheaper, generic versions in to the market, indicating an expectation of the emerging role of generic drugs in the market [2].

The development of generic drugs has important implications regarding individual and public medical health costs for the patient, clinician, government and third-party payer. Provided that generic drugs can save patients and insurance companies substantial costs, generic drugs may be very competitive compared with the brand-name products in the market if they have identical or corresponding pharmacological properties and show similar efficacy and safety for the approved indications of original products.

Paroxetine hydrochloride, available in different formulations – immediate-release, controlled-release and oral suspension – is a widely prescribed selective serotonin reuptake inhibitor (SSRI) that has demonstrated efficacy and safety in a variety of psychiatric disorders, such as MDD, obsessive-compulsive disorder (OCD), panic disorder (PD), generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), social

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Article highlights.

- The development of generic drugs has important implications in relation with individual and public medical health costs for patients, clinician, government and third-party payer.
- The safety, tolerability and efficacy assessments of generic version are not required by authority regulation, which obviously cannot be directly translated into the risk-free switch of the original alternatives in clinical practice.
- FDA had granted final approval to paroxetine mesylate 10-mg, 20-mg, 30-mg and 40-mg strengths for the treatment of major depressive disorder (MDD), obsessive-compulsive disorder (OCD) and panic disorder (PD) in July 2003; recently it has been also approved for patients with generalized anxiety disorder (GAD), in December 2006. However, data indicate that paroxetine mesylate has some potential differences in bio- and clinical-equivalence to paroxetine hydrochloride, although it has not been fully and sufficiently investigated in well-designed clinical trials.
- Whether the efficacy and safety of generic version is substantially comparable to brand-name product needs to be clearly determined in wide clinical experiences of clinicians and patients' acceptability based on data with adequately powered, well-designed, randomized and controlled-comparative clinical trials.

This box summarises key points contained in the article.

anxiety disorder (SAD) and premenstrual dysphoric disorder (PMDD) in the adult population [3,4]. Regarding development of a generic version of paroxetine hydrochloride, the FDA first approved the generic drug, paroxetine mesylate (10-mg, 20-mg, 30-mg and 40-mg tablets) for the treatment of MDD, OCD and PD in July 2003, recently also approved for treating GAD. The principal chemical difference between the two products is that the inactive part of the salt (mesylate or hydrochloride) is separated from the active paroxetine antidepressive molecule in the gastrointestinal tract, leaving only the active paroxetine molecule to be absorbed into the bloodstream and provide the intended therapeutic effect. It has been proposed that paroxetine mesylate has almost identical biochemical and bioequivalence properties to paroxetine hydrochloride. After the launch of generic versions of paroxetine hydrochloride, total paroxetine hydrochloride sales had declined 6% to £553 million in the world market, indicating the significant role and impact of the generic version on the holding power of brand-name products' overall turnover and earnings in the market (**Table 1**) [5].

This review summarizes and focuses on the available data regarding safety, tolerability, efficacy and practical issues dealing with debates between generic and brand-name products, paroxetine mesylate and paroxetine hydrochloride respectively.

2. Pharmacology

2.1 Pharmacokinetics

There have been four pharmacokinetic studies (studies 982413, 009/65/98, 013/78/99 and CPR PA5) conducted by the manufacturer of paroxetine mesylate in healthy volunteers not in patients [6]. The study 982413 showed that paroxetine mesylate 40 mg is bioequivalent to paroxetine hydrochloride 40 mg, while paroxetine mesylate 10 mg failed to prove corresponding pharmacokinetics (C_{max} was similar but not for area under the curve; AUC) with paroxetine hydrochloride 10 mg in the study [6]. However, another study with the 10-mg tablet was needed since current biopharmaceutical guidelines do not require an establishment of bioequivalence at submaximal dose strength and this failure was also observed in the pharmacokinetic study of the 10-mg strength of paroxetine hydrochloride [6].

Studies 009/65/98 and 013/78/99 investigated a bioavailability of paroxetine mesylate to the paroxetine hydrochloride at a dose of 20 mg. In this study, the paroxetine mesylate was almost bioequivalent to paroxetine hydrochloride in C_{max}, T_{max}, $T_{1/2}$ and AUC [7]. The study CPR PA5 investigated a single- and multiple-dose pharmacokinetic profile of paroxetine mesylate 30 mg. In this study, the pharmacokinetic parameters of paroxetine mesylate were quite historically comparable to paroxetine hydrochloride in a single-dose trial with the exception of elimination $T_{1/2}$, while a multiple-dose trial showed some discrepancies between the two products, showing consistently higher pharmacokinetic parameters by at least 1.3 times in paoxetine mesylate strength than in paroxetine hydrochloride strength [7]. More specifically, in a single-dose 30-mg study, the mean elimination $T_{1/2}$ of paroxetine mesylate was twofold higher than paroxetine hydrochloride in historical comparisons [7]. In a multiple-dose 30-mg trial, the C_{max}, C_{min}, AUC and $T_{1/2}$ were 1.3, 1.4, 1.5 and 1.6 times higher than paroxetine hydrochloride in historical comparisons [7]. The main findings of three pharmacokinetic studies for paroxetine mesylate with historical comparison to paroxetine hydrochloride at doses of 10 mg, 20 mg and 40 mg are presented in **Table 2** [6,7]. **Table 2** also provides pharmacokinetic comparison between paroxetine mesylate and paroxetine hydrochloride at a single- and multiple-dose of 30 mg (product labeling relating to pharmacokinetic issue was based on this study). However, again, these are only historical comparisons, not direct comparisons, since there have been no such direct comparison studies.

Paroxetine mesylate is almost completely absorbed after oral dosing of the mesylate salt, and food consumption was not found significantly to affect the absorption of paroxetine mesylate. Paroxetine mesylate is extensively metabolized after oral administration [8].

Approximately 64% of a 30-mg oral solution dose of paroxetine mesylate was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10-day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and < 1% as the parent compound over the 10-day post-dosing period [8]. Paroxetine mesylate has approximately 93 – 95% protein-binding affinity [9,10] and is widely distributed throughout the body, including the CNS. It is metabolized by cytochrome P450 2D6 into inactive metabolites with < 1% as parent

Table 1. Examples of generic drugs of brand-name product, paroxetine in the US market.

Name	Generic manufacturer	Brand name	Approval date
Paroxetine mesylate 10-mg, 20-mg, 30-mg and 40-mg tablets	Synthon Pharmaceuticals, Inc.	Paxil	7 July 2003
Paroxetine hydrochloride tablets 10 mg (base), 20 mg (base), 30 mg (base), and 40 mg (base)	Alphapharm Pty. Ltd	Paxil	8 Mar 2004
Paroxetine hydrochloride tablets 10 mg (base), 20 mg (base), 30 mg (base) and 40 mg (base)	Sandoz, Inc.	Paxil	8 Mar 2004
Paroxetine hydrochloride oral suspension, 10 mg/5 ml	Apotex, Inc.	Paxil oral suspension	4 Dec 2006
Hydrochloride extended-release tablets, 12.5 mg (base) and 25 mg (base)	Mylan Pharmaceuticals, Inc.	Paxil CR	29 June 2007

Data from the FDA. Available from: http://www.fda.gov/.

compound [11]. Nonlinear kinetics probably reflects saturation of CYP450 2D6 at increased paroxetine mesylate doses [12]. Severe renal or hepatic function impairment increases plasma paroxetine mesylate concentrations by twofold [10,11].

The paroxetine hydrochloride drug–drug interaction clinical studies had suggested that substrates of CYP 2D6 such as desipramine and atomoxetine may be inhibited by paroxetine mesylate, which may be also same for paroxetine mesylate. In particular, some antipsychotics are contraindicated to combine with paroxetine mesylate owing to possible increased plasma concentration of the drug [8,13].

2.2. Pharmacodynamics

There have been no proven independent pharmacodynamic studies for paroxetine mesylate. Hence, pharmacodynamic property of paroxetine mesylate should be borrowed from studies of paroxetine hydrochloride. Paroxetine seems to have the highest affinity for human serotonin transporters compared with other marketed SSRIs, indicating that paroxetine is the most potent SSRI today [14,15]. It is also known to be a modest inhibitor of human norepinephrine transporter as well as being a weak inhibitor of dopamine transporter [16]. Preclinical studies established that paroxetine has modest affinity for muscarinic cholinergic receptors and was found to have very weak or no affinity for histaminic, alpha or beta adrenergic, dopaminergic or serotonergic (5-HT1, 5HT2) receptors [17].

3. Toxicology

Preclinical studies with rats were conducted to determine the toxicology findings for paroxetine mesylate [13]. In these studies, toxicologic parameters of paroxetine mesylate were found to be similar to those of paroxetine hydrochloride, in which decreased body weight, transient decrease in food consumption, some clinical signs such as sensitivity to touch, salivation and respiratory sounds [13]. As for organ toxicity, lungs and lymph nodes were involved with changes such as vacuolization and histocytosis [13]. Decreased weight of spleens, heart and liver indicated potential damage; however, these were not accompanied by obvious changes in clinical chemistry, hematology or histopathology [13].

4. Teratogenecity

Preclinical studies have indicated that paroxetine mesylate was not mutagenic, which is in line with paroxetine hydrochloride [13].

5. Carcinogenecity

There have been no formal studies regarding the potential carcinogenicity for paroxetine mesylate [13].

6. Reproductive toxicology

There have been no formal studies regarding the reproductive toxicology for paroxetine mesylate. The FDA has determined that exposure to paroxetine hydrochloride in the first trimester of pregnancy may increase the risk for congenital malformations, particularly cardiac malformations [18]. The manufacturer, GlaxoSmithKline, has recently changed paroxetine's pregnancy category from C to D and added new data and recommendations to the warnings section of paroxetine's prescribing information [19,20]. This point should be borne in mind when prescribing paroxetine mesylate as well.

7. Other safety and tolerability profiles

There have been no officially conducted placebo-controlled clinical trials for paroxetine mesylate for patients with approved indications. In addition, paroxetine, the active ingredient of paroxetine mesylate, is the same for paroxetine hydrochloride. The pharmacokinetic and pharmacodynamic properties are considered to be almost identical in both the generic version and brand-name product. The manufacturer of paroxetine mesylate did not conduct detailed such studies since the regulatory agency and available biopharmaceutical guidelines do not require those studies for the generic version. Hence we may assume that other safety issues might be similar

Table 2. The four pharmacological studies for paroxetine mesylate in healthy volunteers (historical comparison with each dose of paroxetine hydrochloride).

Studies and parameters	Paroxetine mesylate		Paroxetine hydrochloride	
Study 982413 (*a 2-part pharmacokinetic study*)				
40 mg				
C_{max} (ng/ml)	24.4		26.7	
T_{max} (h)	6.3		6.2	
$T_{1/2}$ (h)	15.3		15.1	
AUC (ng*h/ml)	644.7		659.4	
2 × 10 mg				
C_{max}	6.4		5.9	
T_{max}	6.2		5.8	
$T_{1/2}$	13.4		12.7	
AUC	158.3		144.9	
Study 013/78/99 (*20 mg*)				
C_{max}	4.1		4.2	
T_{max}	5.9		5.7	
$T_{1/2}$	13.8		13.6	
AUC	90.6		95.3	
Study 009/65/98 (*20 mg*)				
C_{max}	3.7		3.9	
T_{max}	5.4		5.2	
$T_{1/2}$	13.7		13.3	
AUC	71.6		72.5	
Study CPR PA5 (*20 mg*)				
	Single dose	Multiple dose	Single dose	Multiple dose
C_{max}	13.0	81.3	13.7	61.7
T_{max}	5.6	8.1	4.8	5.2
$T_{1/2}$	23.5	33.2	9.8	21.0
AUC	176	1509	175	1021
C_{min} (ng/ml)	NA	43.2	NA	30.7

NA: Not applicable; Data represent mean number.
Data from the FDA. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist.

to those of paroxetine hydrochloride. The detailed safety and tolerability profiles are presented elsewhere [18].

8. Efficacy

There have been no officially conducted placebo-controlled clinical trials for paroxetine mesylate for patients with approved indications. In addition, we have at present no such information regarding direct comparative studies between the generic version and brand-name product. Similarly, safety and tolerability issues: all available efficacy information incorporated in product labeling was completely based on those from previously proven placebo-controlled registry clinical trials with the brand-name product, paroxetine hydrochloride [4]. Paroxetine mesylate (10-, 20-, 30- and 40-mg strengths) is now consecutively approved for the treatment of MDD, OCD, PD and GAD [8].

9. Practical and clinical issues between paroxetine mesylate and paroxetine hydrochloride

So far, there have been no systematic studies comparing efficacy or safety of paroxetine mesylate with paroxetine hydrochloride. However, some concerns relating to the efficacy and safety of switching from paroxetine hydrochloride to paroxetine mesylate in a form of case series [21] or case report [22] have emerged. These might be naturally expected since paroxetine mesylate preparation involves a different type of salification process from that used in the preparation of paroxetine hydrochloride, giving potential problems relating to efficacy, tolerability and toxicity [23].

The first case report showed that depression patient A, comorbid with panic attack, who had completely remitted (no

experience of recurrence on paroxetine hydrochloride) for a long time (not specified but described for several years) on paroxetine hydrochloride 30 mg/day, suddenly developed an adverse event (itching) that the patient had not previously experienced; he did not have any potential underlying dermatological conditions or medication [22]. The patient's depression continued to worsen. This situation occurred a day after a pharmacist switched the patient's therapy from paroxetine hydrochloride to paroxetine mesylate. Upon readministration of paroxetine hydrochloride, the patient's mood steadily improved and itching never recurred. To confirm the causative relationship with paroxetine mesylate, under mutual agreement between clinician and patient, paroxetine hydrochloride was switched to paroxetine mesylate again, after which the patient had exactly the same adverse event and efficacy problem. These were immediately reversed by switching from the generic version to paroxetine hydrochloride.

Subsequent case-series reports [21] involving three (B, C and D) patients switched from original or one generic paroxetine to generic or different generic paroxetine respectively also suggest similar interesting issues. **Table 3** summarizes the cases of patients A – D, with clinical implications (**Table 3**).

Although these reports were not controlled clinical trials or direct comparison studies using a generic version and original product, they indicate several things to be considered in the switch of generic drugs from original product and even switching from one generic version to a different generic medication.

The current biopharmaceutical guidelines and authority agency regulation do not require any further placebo-controlled clinical trials investigating efficacy and safety if the generic version meets the criterion of bioequivalence to the original product: the FDA declares that pharmaceutical equivalents only are therapeutically equivalent, and pharmacokinetic data are all that is usually required to determine therapeutic equivalence (C_{max} and AUC mean values ranging from 80 to 125% compared with those of the brand-name product) [24]. The problem of this concept is that the FDA accepts -20% to +25% variation in C_{max} and AUC in compounds that are considered bioequivalent, since it is less strict than its -5% to +5% criterion for the brand-name product [23].

Another point is that all cases reported herein are not notified to clinicians and patients, which are very important in the compliance and monitoring of a patient's clinical status. This issue may be different between countries according to their own medical regulations. For example, pharmacists may not change a brand-name product without notification to the clinician in South Korea, while other countries may allow a pharmacist to replace the original prescription with a generic version [25]. In fact, inadequate efficacy and unwanted adverse events mainly explain the reasons for patients' drug compliance issues [26]. In addition, according to a patient survey, education on overall facts related to medications is also involved in enhancing drug compliance [27].

Usually, pharmacokinetic studies necessary to prove bioequivalence are conducted only in healthy subjects who might be fundamentally different from the patient population in terms of overall biophysical conditions. For instance, volunteers enrolled in paroxetine mesylate pharmacokinetic studies ranged in age from 18 to 45 years and were medically healthy. By contrast, based on large-scale epidemiological studies [28,29], comorbid psychiatric and medical illness are very likely to occur in psychiatric patients regardless of diagnosis, showing that actual patients may have different properties and capacities in drug–drug interaction and pharmacokinetics.

The requirements for bioequivalence of generic drug to brand-name product are 80% to 125%. These insufficient requirements have potential problems such that replacement with the generic version may cause unexpected reduction or inability to maintain efficacy, and different profiles of adverse events compared with the original brand [24]. Hence, we may also expect that insufficient criteria for bioequivalence would negatively affect patients' drug compliance and clinicians' proper judgment on patients' clinical status [21].

Finally, as seen in **Table 3**, all patients involved in the worsening of depressive symptoms had comorbid AXIS I disorders such as anxiety disorders and showed abrupt relapse immediately after switching to generic paroxetine from brand-name paroxetine without notification to clinician and patient. This indicates that clinicians have to monitor whether the medication is same that they prescribed to their patients as well as pay more attention to changes of symptoms in their patients if they were informed of a medication change by the pharmacist.

Hence, whether or not generic formulations would adequately replace the original version in terms of efficacy and safety will be properly determined by well-designed, randomized, comparative studies between generic and brand-name products. In addition, pharmacokinetic studies for generic versions proving their bioequivalence should be also taken in the patient population.

10. Conclusion

Despite the insufficient evidence comparing generic and brand-name versions, currently available small case reports clearly propose that existing regulatory procedures to approve generic version only require essential bioequivalence, have limitations and fail to meet stricter scientific and clinical demands.

11. Expert opinion

Aforementioned issues have been also well described in studies with clozapine [30-32], diazepam [33], phenytoin [34], carbamazepine [35] and valproate [36-39]. These studies only involved small samples and were not well controlled but consistently indicate that bioequivalence and clinical equivalence of generic drugs may be potentially different compared with brand-name products. In particular, generic antiepileptic drugs have been the subject of persistent concerns regarding potential therapeutic in-equivalence, and recent data have also questioned the actual cost savings associated with generic

Table 3. Description of patients who had efficacy and adverse event from switching to generic paroxetine.

Patient	Description
A	
Sex	Male
Age	29 years
Diagnosis	Major depressive disorder (MDD) with panic symptoms
Initial treatment	Paroxetine hydrochloride 30 mg/day
Switching to	Paroxetine mesylate 30 mg/day
Problems	Recurrence of MDD, itching
How solved	Reinstating paroxetine hydrochloride; confirmation of causal relationship with switching to paroxetine mesylate by on and off therapy with paroxetine mesylate
Implication	The first case report of adverse event and recurrence by switching to generic paroxetine from original paroxetine; nerver-experienced adverse event (AE) may be developed; re-administration of original paroxetine may resolve the problems
B	
Sex	Female
Age	26 years
Diagnosis	Generalized anxiety disorder (GAD); panic disorder (PD); MDD
Initial treatment	Paroxetine hydrochloride 30 mg/day
Switching to	Generic paroxetine
Problems	Recurrence of MDD and GAD symptoms
How solved	Increase of generic paroxetine from 40 mg/d to 50 mg/d
Implication	Switching to different form of generic paroxetine may also make similar efficacy problem seen in cases switching from original paroxetine to generic version; individual generic may have different pharmacokinetic profiles possibly affecting efficacy; may need more dose when switching to different generic drugs
C	
Sex	Female
Age	44 years
Diagnosis	PD; MDD; social anxiety disorder (SAD)
Initial treatment	Generic paroxetine 30 mg/day
Switching to	Different generic paroxetine
Problems	Severe aggravation of MDD symptoms and development of panic attacks
How solved	Switching to the original generic paroxetine
Implication	Re-administration of original generic version may resolve the problems
D	
Sex	Female
Age	28 years
Diagnosis	SAD; MDD; post-traumatic disorder (PTSD)
Initial treatment	Paroxetine hydrochloride 40 mg/day
Switching to	Generic paroxetine
Problems	Significant increase in SAD and PTSD symptoms; sudden onset of MDD symptoms
How solved	Increase of generic paroxetine from 40 mg/day to 60 mg/day
Implication	Same as patient B

Data from [21,22].

substitution in seizure patients [40]. According to a recent large-scale survey with neurologists (n = 6420), 67.8% neurologists reported breakthrough seizures after a switch from a brand-name to a generic antiepileptic drug, while only approximately one third of them did not. More than half of neurologists reported increased side effects in their patients after a switch from a brand-name to a generic antiepileptic drug. In addition, only one fifth of neurologists agreed that the FDA standards for antiepileptic drug bioavailability are sufficiently narrow, while more than 80% of them disagreed [41].

Other generic antidepressants such as fluoxetine [42,43], citalopram [21,44] and bupropion [45] were also questioned about their efficacy and adverse events comparing their brand-name products. In 2007, the FDA received 85 post-marketing reports in which patients who switched from bupropion XL 300 mg to Teva's generic bupropion formulation (budeprion XL 300 mg) experienced an undesirable effect. In this report, a number of cases also reported the new onset or worsening of side effects. The reported side effects were consistent with the adverse effects in labeling for bupropion products. More than half of the patients who switched back to bupropion XL 300 mg reported improvement of depression and/or abatement of side effects [45]. However, after re-examination of these data and pharmacokinetic equivalence profile between generic and brand-name bupropion, the FDA concluded that the reports of switch problems are more related to the natural course of MDD; although there are small differences in the pharmacokinetic profiles of the two formulations, they are not outside the established boundaries for equivalence nor are they different from other bupropion products known to be effective. In addition, bioequivalence of generic drugs compared with original version is not always proven. Recently, venlafaxine (effexor) XR/Novo-venlafaxine XR 75 mg and citalopram (Celexa)/Gen-citalopram 40 mg were studied in a randomized crossover design [46]. In this study, the C_{max} values (150%) were not in the range of 80 – 125%, which is the FDA standard for the approval of bioequivalence. The concentration of the active metabolite of venlafaxine (O-desmethyl-venlafaxine) was also significantly increased in subjects treated with a generic version (+43% higher in the generic group at 3 h; +48% higher at 5 h). Subjects taking Novo-venlafaxine reported three times more side effects than those taking effexor XR [46]. Gen-citalopram seemed to be bioequivalent to Celexa in this study; the efficacy was also challenged in the previous study that suggested potential differences even within a given pharmaceutical company [44]. To re-iterate, safety, tolerability and efficacy assessments are not required by authority regulation, which obviously cannot be put into evidence in a proper bioequivalence study whereby a single dose is administered. This is yet another pitfall of the use of generics. It is in the long-term that large differences may be seen. The data in **Table 2** clearly show this caveat. The C_{max} after multiple doses is 81.3 versus 61.7 h and also the T_{max} was achieved after 8.1 (multiple doses) versus 5.2 (single dose) hours.

The relapse of depressive symptoms during maintenance antidepressant treatment in the naturalistic setting has occurred in 9 – 57% of patients in published trials. Loss of placebo effect, pharmacologic tolerance, increase in disease severity, change in disease pathogenesis, the accumulation of a detrimental metabolite, unrecognized rapid cycling, and prophylactic inefficacy are possible explanations for the relapse [47]. These trends were replicated in a number of studies regardless of using brand-name or generic drugs in controlled trials or naturalistic studies [48-50]. For example, approximately 10% of MDD patients recur during the second month of continuation pharmacotherapy, indicating that there has been a strong possibility of recurrence during their natural treatment course [49]. These rates possibly show that the reported cases of worsening of symptoms following a switch to generic versions are not due to the small pharmacokinetic differences between the generic and brand-name products [45].

In addition, instability in switching to generic versions does not always occur since we also see a number of problem-free patients in this transition period. In fact, a number of studies investigating interchangeability in patients treated with clozapine have shown the drug's safety, stating that switching to generic clozapine may show no significant differences in efficacy and safety but in addition may result in reduction in health care use and pharmacy cost [51-53].

Taken altogether, the stance of clinicians may not be clearly established in this matter. We clinicians need to stand in a neutral position to meet the best available risk and benefit in switching from brand-name products to generic versions. Therapeutic equivalence does not exactly correspond to therapeutic identicalness and this will be the same among generic versions to one original product [54]. In addition, the quality of all generics could not be guaranteed across products at all times [54]. Whether the efficacy and safety of paroxetine mesylate is substantially comparable to brand-name product paroxetine hydrochloride needs to be determined through wide clinical experiences of clinicians and patients' acceptability based on data with adequately powered, well-designed, randomized and controlled comparative clinical trials.

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Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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