Antidepressant medications: The FDA-approval process and the need for updates

Conor Hanrahan, PharmD, BCPS[1]
James P. New, PharmD, BCPS[2]

[1] PGY2 Drug Information Resident, Department of Pharmacy Services, Medical University of South Carolina
[2] Clinical Specialist, Medication Use Policy and Informatics, Department of Pharmacy Services
Medical University of South Carolina

ABSTRACT

Antidepressant drug development first began in the mid-twentieth century with the discovery of monoamine oxidase inhibitors and tricyclic antidepressants. Soon after, additional molecular targets and drug entities were created, eventually leading to the development of selective serotonin reuptake inhibitors. Today, antidepressants now rank among the top 10 most commonly used medications in the United States (US) and account for over $11 billion in annual sales. To help ensure the safety and efficacy of these commonly used products, in 1977 the US Food and Drug Administration (FDA) created guidelines to standardize antidepressant studies and the approval process. Although many of the recommendations outlined by FDA are still relevant, the document remains vague when describing key aspects of antidepressant trial design and much of the clinical information is outdated by today's standards. This paper will provide a general overview of the FDA-approval process, summarize FDA's position related to antidepressant trial design, and discuss the need for updates in the approval process.

KEYWORDS

Food and Drug Administration, antidepressant, depression

HISTORY OF ANTIDEPRESSANT DRUG DEVELOPMENT

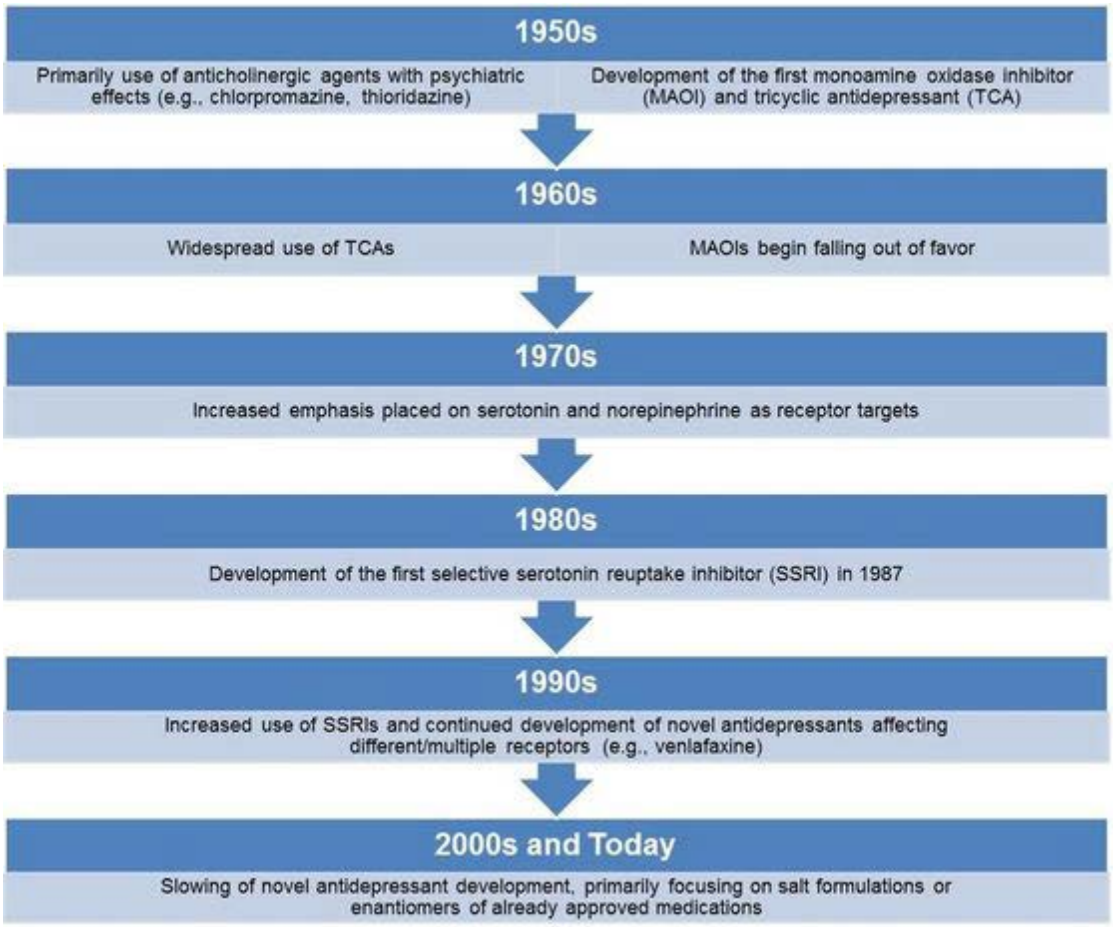
Chemical agents have been known to cause antidepressant effects since the time of the ancient Greeks when Poppy was believed to help relieve "sorrow." This perceived effect, of course, was due to the presence of opium. "Opium cures" were even utilized well into the 19th century as a treatment of depression. Alternative agents such as dinitrile succinate, hematoporphyrin, and reserpine had begun to be used at this point in history as well.[1] There is also evidence of amphetamines being utilized in the 1930s as treatment for patients with depression.[2] However, it was not until the mid-twentieth century that major events in modern antidepressant drug development began.

In the early 1950s, patients with depression were largely treated with anticholinergic agents known to have psychiatric effects (e.g., chlorpromazine, thioridazine, levomepromazine).[1] However, drug development took a leap with the discovery of 2 specific agents: the monoamine oxidase inhibitor (MAOI), iproniazid, and tricyclic antidepressant (TCA), imipramine. With these agents came a better understanding of the role that endogenous chemicals—such as dopamine, norepinephrine, and serotonin—play in the stabilization of mood. The 1960s brought a more widespread use of the TCAs due to the development of other agents in this class (e.g., amitriptyline, desipramine) that had fewer side effects than their predecessor. At the same time, MAOI agents began to fall out of favor due to the discovery of several adverse effects, dietary restrictions, and drug interactions.[1,3,4]

As psychiatric research continued into the 1970s, discussion and debate revolved around the importance of norepinephrine and serotonin (either in congruence or individually) for the successful treatment of patients with depression.[3] However, by the 1980s, drug development began to shift toward serotonin as a key target in antidepressive therapy. This change may have been partially driven by the approval (1985) and quick withdrawal (1986) of the norepinephrine/dopamine uptake inhibitor, bupropion, due to seizures.[5,6] Soon after in 1987, fluoxetine became the first US Food and Drug Administration (FDA)-approved selective serotonin reuptake inhibitor (SSRI).[7]

At this time, prescribing of antidepressant medications was becoming more common among primary care physicians. This shift has been attributed to the improved tolerability of SSRIs as compared with previously

Figure 1. Major Developments In Antidepressant Therapy



developed drugs. Antidepressant agents in this period also began to be utilized for indications outside of depression (e.g., anxiety).[3] Additionally there was further development of alternative medications that affect both norepinephrine and serotonin, such as venlafaxine.[1] These events likely contributed to the growing prevalence of antidepressant use in the United States, which increased by approximately 400% from 1988 to 2008.[8]

More recently, novel antidepressant drug approvals appear to have slowed as several recently approved medications are chemical enantiomers or different salt formulations of already approved drugs (e.g., desvenlafaxine, escitalopram, bupropion hydrobromide).[7] Additionally, it has been suggested that while tolerability of these agents has improved since the 1950s, efficacy has not.[1,4] Perhaps further compounding this cessation of novel drug development are outdated antidepressant approval guidelines from the FDA, which do not incentivize manufacturers to achieve greater levels of symptom improvement or target novel disease pathways. This article will serve as a primer of the FDA-approval process, review factors the FDA considers when evaluating antidepressant medications, and discuss the need for updated guidelines outlining antidepressant efficacy.

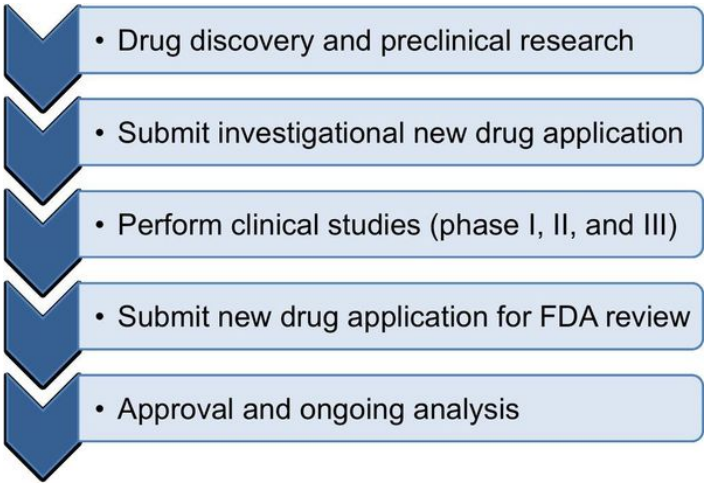
OVERVIEW OF THE DRUG APPROVAL PROCESS

The FDA is responsible for ensuring the safety and efficacy of drugs, vaccines, biologic products, dietary supplements, medical devices, foods, and cosmetics.[9] Among the branches of FDA dealing with medical products, the largest is the Center for Drug Evaluation and Research (CDER), which is responsible for reviewing and approving prescription drugs in humans.

Figure 2 provides an overview of the drug approval process, which typically starts with the creation of a new molecular entity (NME). These products either contain an entirely new active moiety that has not yet been approved by FDA (also called a "new chemical entity") or contain an active moiety that is closely related to a previously approved product (such as a different salt or ester).[10,11] A drug developer must then test the pharmacologic activity of the NME in various laboratory and animal models. Once the developer is ready to test

the molecule in humans, an Investigational New Drug (IND) application must be submitted to CDER. This application contains preclinical data regarding animal pharmacology and toxicology studies, manufacturing considerations (e.g., stability, production methods), and detailed protocols for the proposed clinical studies in human subjects.[12]

Figure 2. The Drug Approval Process



After submitting the IND application, drug developers must perform adequate, well-controlled clinical trials to prove that the new product is safe and effective. In general, these studies should be approved by an institutional review board; provide a protocol describing the study rationale, objectives, selection criteria, sample size, and methods of analysis; use a study design that permits a valid comparison with a control (e.g., placebo control, active control, dose-comparison control, historical control); employ methods to ensure the validity of the data obtained (e.g., measures to minimize bias); and provide an analysis of the results which is adequate to assess the effects of the drug.[13,14]

These clinical evaluations are almost always conducted in phases. Phase I studies are primarily conducted in healthy subjects and are intended to determine the pharmacokinetic effect of the drug in humans, the levels of toxicity, and the appropriate dosage range. Phase II investigations consist of small controlled trials designed to demonstrate effectiveness and relative safety in a limited number of patients. Finally, phase III trials are more extensive controlled studies intended to gather additional effectiveness data for specific indications and more precise safety information.[14] Generally, the FDA requires at least 2 adequate and well-controlled studies demonstrating "substantial evidence" of efficacy in order to support approval.[15] By this standard, it is important to note that the number of "negative" studies does not necessarily affect approval.

After conducting these trials and gathering enough evidence to prove the safety and efficacy of the study compound, the drug developer must submit a New Drug Application (NDA) to CDER. This NDA is the mechanism by which the drug developer "formally proposes that the FDA approve a new pharmaceutical for sale and marketing in the United States."[16] Building upon the IND, the information submitted with the NDA allows CDER to verify the drug's safety and efficacy for its proposed indication, verify the appropriateness of the proposed labeling (i.e., package insert), and assess whether the proposed manufacturing practices are adequate to ensure the strength, quality, and purity of the product.[16]

CONSIDERATIONS FOR THE CLINICAL EVALUATION OF ANTIDEPRESSANT DRUGS

The approval of antidepressant medications follows much of the same principles outlined above. However, FDA has created specific guidelines for the evaluation of antidepressant drugs with the intent of standardizing and clarifying the planning, monitoring, analysis, and evaluation of antidepressant studies.[17] These guidelines were first published in 1977 and have not been updated or revised since that time.[18] Nevertheless, the document still serves as a loose framework for antidepressant drug development in the United States.

Table 1 summarizes several requirements discussed in the FDA guidance for phase I, II, and III studies. Overall, the guidance reinforces general best practices for conducting a study, such as evaluating the new medication in a wide variety of patients and encouraging a comparison with an active or placebo control. However, the document remains vague regarding key aspects of antidepressant study design and methodology. For instance, the duration of phase II and III studies is very broad, noting that they may last days to weeks, with at least 1 study being at least 6 weeks or longer.[17]

Similarly, FDA does not make a specific recommendation regarding the assessment scale used to evaluate treatment effects, stating that, "Investigators are encouraged to use scales which have already been used in drug research."[17] FDA notes that experience exists with scales such as the Raskin, Beck, Wittenborn, Minnesota Multiphasic Personality Inventory, Hamilton, Zung, Overall, Spitzer, Symptom Check List, and Clyde Mood Scale, but does not make a specific recommendation as to which scale is preferred. FDA continues, vaguely stating that, "No one technique in itself is considered

Table 1. Summary of FDA Guidelines for the Clinical Evaluation of Antidepressant Drugs[17]

	Phase I Study	Phase II Study	Phase III Study
Objective	Determine human tolerance and pharmacokinetic parameters (absorption, distribution, metabolism, and excretion)	Identify potentially responsive therapeutic conditions, estimate appropriate clinical dosage and duration, and evaluate possible adverse effects	Confirm efficacy of antidepressant activity and potential side effects in various patient populations
Subjects	Generally, normal, healthy volunteers age 21 and over who should not require concomitant medications* Women of childbearing potential, children, and individuals with serious diseases should usually be excluded	In early phase II studies, subjects should be heterogeneous and mimic those in phase I studies In late phase II studies, subjects should be as homogeneous as possible with regard to factors such as age, sex, weight, setting, etc. For treatment of depression as a syndrome (rather than a symptom of another disease), patients should "usually manifest a depressed mood plus a significant number (4-5) of associated symptoms" (Figure 3)**	A variety of populations (with regards to age, sex, diagnostic category, social class, treatment setting, etc) may be studied Populations within each study should be as homogeneous as possible
Setting	Confined setting with close supervision and treatment on a 24-hour basis	Inpatient setting is preferred for early phase II studies, while other settings (e.g., outpatient) are acceptable in late phase II studies	Inpatient, outpatient, private practice, etc are acceptable
Study Design	Single-dose or multiple-dose escalation studies Double-blind, parallel group, placebo-controlled studies are preferred Subjects should undergo a washout period prior to receiving study drug	Uncontrolled, open label studies may be acceptable for early phase II evaluations At least some phase II studies should be compared to a matching placebo or active control (parallel groups, crossover, and other designs may be used) Subjects should undergo a washout period prior to receiving study drug	At least 3 to 5 studies should compare the new compound with a placebo or active control with demonstrated efficacy Long-term safety studies are encouraged; these data may also be obtained from multiple studies, rather than from a single trial
Duration	Days to weeks	Days to weeks, with at least 1 study being 6 weeks or longer	Similar to phase II requirements; long-term safety studies should be least 3 to 6 months
Sample size	Variable, but small samples (as little as 6 subjects) are permitted in an open trial	Variable, but a minimum of 20 patients per treatment group in late phase II studies	Variable, but at least 30 to 50 patients in each group for controlled trials
Dosages	First doses in early studies should be minimal (e.g., 1/5th the maximal nontoxic dose in animals)	Doses in open trials can be increased until a satisfactory therapeutic response is observed Doses should usually be fixed in double-blind, controlled studies; however, a range may be used and adjusted according to specified criteria	Similar to phase II studies
Assessments	Repeated and extensive physical examination, vital signs, laboratory tests (involving liver, renal, and cardiovascular systems), and other tests as needed depending on the type of drug and preclinical study data	Similar to phase I studies Severity of illness should be described using global scales "Investigators are encouraged to use scales which have already been used in drug research" (e.g., Raskin, Beck, Wittenborn, MMPI, Hamilton, and Zung) Report socio-economic and clinical characteristics, as well as previous therapies (e.g., electroconvulsive therapy)	Similar to the features of phase I and II studies

*FDA recognizes that tolerability and side effect profiles may have little relevance in healthy volunteers when compared with some psychiatric patients
**FDA recognizes that defining and diagnosing depression is difficult and often subjective

sufficient. Not all techniques are required," implying that several assessment methods should be used.[17] Furthermore, FDA does not offer guidance regarding the level of improvement or change in rating scale score necessary to show a benefit. There is also no mention of response or remission rates being considered as part of the efficacy analysis. These considerations have been incorporated into more recent FDA guidance documents on drug development, such as those for systemic lupus erythematosus, which define reductions in disease severity and clinical response.[19]

Given the age of the guidelines, it is also not surprising that much of the clinical information in the document is outdated. For example, when describing treatment comparators that should be used to test against the study compound in phase III trials, the guidance suggests TCAs and MAOIs.[17] Today, these agents are generally reserved for patients who do not respond to therapy with an SSRI or serotonin norepinephrine reuptake inhibitor.[20] Similarly, the diagnosis of major depressive disorder (MDD) does not reflect the current recommendations outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.[21] The FDA guidance notes that defining depression is often subjective, and is not overly specific with respect to the number of symptoms or timeframe required for diagnosis (Figure 3).

Figure 3. Diagnosis of Depression in FDA Antidepressant Guidance for Industry, 1977[17]

Depressed mood (characterized as sad, low, blue, despondent, hopeless, or gloomy), plus a significant number (4-5) of the associated symptoms shown below.

- Anhedonia (inability to experience pleasure)
- Poor appetite or weight loss
- Sleep difficulty (insomnia or hypersomnia)
- Loss of energy, fatigue, lethargy
- Agitation
- Retardation
- Decrease in libido
- Loss of interest in work and usual activities
- Feelings of self-reproach or guilt
- Diminished ability to think or concentrate such as slowed thinking or mixed-up thought
- Thoughts of death and/or suicide attempts
- Feelings of helplessness and hopelessness
- Anxiety or tension
- Bodily complaints

CONCLUSION

The development and use of antidepressant medications has increased considerably since the 1950s, with antidepressants now ranking among the top 10 most commonly used therapeutic classes in the United States and accounting for $11 billion in annual sales.[22] However, despite this wide spread use of antidepressants, novel drug development has slowed in recent years. Aside from the approval of vilazodone (2011), and vortioxetine (2013) with 5-HT_1 agonist activity, the majority of antidepressants developed since 2000 are merely salt formulations or enantiomers of already approved drugs. Perhaps mimicking this trend, the FDA guidelines for approving new antidepressants has remained unchanged for the past 30 years, despite continued advancements in clinical practice. In fact, the guidelines were developed a full 10 years before the creation of SSRIs, which have now become a first-line treatment for MDD.

Although FDA has done much to regulate the development of other drug classes, such as oncology agents, the antidepressant guidelines do little to actually standardize approval requirements. Outcome measures are particularly vague, with FDA providing little guidance as to the preferred assessment scale used to measure drug efficacy. This lack of standardization has created inconsistency between antidepressant clinical trials. For example, the phase III studies used to approve desvenlafaxine were based on changes in the 17-item Hamilton Rating Scale for Depression, while the approval of escitalopram was primarily based on the Montgomery Asberg Depression Rating Scale.[23,24] Furthermore, the guidance does not address the level of improvement or change in rating scale score necessary to show a benefit. Such inconsistencies have made it difficult for health care practitioners to assess the value of these medications as they enter the marketplace.

Given that FDA is charged with ensuring drug efficacy, it is important that these antidepressant guidelines remain up to date. Doing so may help stimulate the development of drugs that offer a clinically meaningful improvement in outcomes, as defined by today's standards of psychiatric practice. It may also be reasonable for FDA to require head-to-head trials evaluating patient-oriented outcomes of efficacy or safety prior to approval of "me too" products. Additionally, establishing a consensus on the number and type of depression assessment scales utilized for FDA-approval would help with standardization and the delineation of clinically useful interventions. For new agents not displaying a significant, clinically meaningful safety benefit, minimum differences in treatment effects over current therapies should be established as well.

REFERENCES

1. Ban TA. Pharmacotherapy of depression: a historical analysis. J Neural Transm. 2001;108(6):707-16. PubMed PMID: 11478422.
2. Rasmussen N. Making the first anti-depressant: amphetamine in American medicine, 1929-1950. J Hist Med Allied Sci.
3. 2006;61(3):288-323. DOI: 10.1093/jhmas/jrj039. PubMed PMID: 16492800.
4. Lieberman JA. History of the Use of Antidepressants in Primary Care. Primary Care Companion J Clin Psychiatry. 2003;5[suppl 7]:6-10.
5. Abraham J, Davis C. Drug evaluation and the permissive principle: continuities and contradictions between standards and practices in antidepressant regulation. Soc Stud Sci. 2009;39(4):569-98. PubMed PMID: 19848109.
6. Burroughs welcome's voluntary withdrawal of Wellbutrin. The Pink Sheet [Internet]. 1986 Mar 17 [cited 2013 Sept 3]; article 00480110016. Available from: http://www.elsevierbi.com/publications/the-pink-sheet/48/011/burroughs-wellcomes-voluntary-withdrawal-of-wellbutrin.
7. Burroughs welcome to relaunch antidepressant Wellbutrin in mid-July after aborted launch in 1986; FDA-approved labeling includes data on seizure risk. The Pink Sheet [Internet]. 1989 July 3 [cited 2013 Sept 3]; article 00510270001. Available from: http://www.elsevierbi.com/publications/the-pink-sheet/51/027/burroughs-wellcome-to-relaunch-antidepressant-wellbutrin-in-midjuly-after-aborted-launch-in-1986-fdaapproved.
8. US Food and Drug Administration. [Internet]. Silver Spring (MD): US Food and Drug Administration; [updated 2013 July 15]. Drugs@FDA: FDA Approved Drug Products; [cited 2013 July 19]. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Search_Drug_Name
9. Pratt LA, Brody DJ, Gu Q. Antidepressant use in persons aged 12 and over: United States, 2005–2008. NCHS data brief, no 76. Hyattsville, MD: National Center for Health Statistics. 2011.
10. US Food and Drug Administration. [Internet]. Silver Spring (MD): US Food and Drug Administration; [updated 2013 July 15]. About FDA: FDA Fundamentals; [updated 2013 May 6; cited 2013 July 19]. Available from: http://www.fda.gov/AboutFDA/Transparency/Basics/ucm192695.htm
11. US Food and Drug Administration [Internet]. Silver Spring (MD): US Food and Drug Administration; [updated 2013 July 15]. New Drugs at FDA: CDER's New Molecular Entities of 2013; [updated 2013 July 15; cited 2013 July 19]. Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/default.htm
12. US Food and Drug Administration, Center for Drug Evaluation and Research [Internet]. Silver Spring (MD): US Food and Drug Administration; [updated 2013 July 15]. Orange Book Preface, 32nd Edition; [updated 2012 Feb 3; cited 2013 July 19]. Available from: http://www.fda.gov/drugs/developmentapprovalprocess/ucm079068.htm
13. US Food and Drug Administration [Internet]. Silver Spring (MD): US Food and Drug Administration; [updated 2013 July 15]. Investigational New Drug (IND) Application; [updated 2013 April 25; cited 2013 July 19]. Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm
14. US Food and drug Administration, Code of Federal Regulations [Internet]. Silver Spring (MD): US Food and Drug Administration. Adequate and well-controlled studies. Title 21, Section 314.126. Available from: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm
15. US Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry: General considerations for the clinical evaluation of drugs. Rockville (MD): US Food and Drug Administration; 1997 Jan 1. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071682.pdf
16. US Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for Industry: Providing clinical evidence of effectiveness for human drugs and biological products. Rockville (MD): US Food and Drug Administration; 1998 May. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078749.pdf
17. US Food and Drug Administration [Internet]. Silver Spring (MD): US Food and Drug Administration; [updated 2013 July 15]. New Drug Application (NDA); [updated 2013 Feb 21; cited 2013 July 19]. Available from: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm
18. US Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry: Guidelines for the clinical evaluation of antidepressant drugs. Rockville (MD): US Food and Drug Administration; 1977 Feb. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071299.pdf
19. Drug Information Specialist KC (Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Information, Silver Spring, MD). Letter to: Hanrahan, Conor (Medical University of South Carolina, Charleston, SC). 2013 July 3.
20. US Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for Industry: Systemic lupus erythematousus—developing medical products for treatment. Rockville (MD): US Food and Drug Administration; 2010 June. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072063.pdf
21. American Psychiatric Association. Practice guidelines for the treatment of patients with major depressive disorder. 3rd ed. Arlington: American Psychiatric Association; 2010. Available from: http://www.psychiatry.org/practice/clinical-practice-guidelines
22. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA, American Psychiatric Association, 2013. Web. [19 July 2013: 1 June 2013]. dsm.psychiatryonline.org
23. Lindsley CW. The top prescription drugs of 2011 in the United States: antipsychotics and antidepressants once again lead CNS therapeutics. ACS Chem. Neurosci. 2012;3(8):630-1. DOI: 10.1021/cn3000923. PubMed PMID: 22896807; PubMed Central PMCID: PMC3419448.
24. Lexapro [Package Insert]. St. Louis, MO. Forest Laboratories, Inc.; 2012 Dec.
25. Pristiq [Package Insert]. Philadelphia, PA. Wyeth Pharmaceuticals, Inc.; 2013 Feb.

How to cite this article
Hanrahan C, New JP. Antidepressant medications: The FDA-approval process and the need for updates. Ment Health Clin [Internet]. 2014;4(1):11-6. Available from: http://dx.doi.org/10.9740/mhc.n186950