Odds and Ends in Psychopharmacology From the Past 10 Years

ABSTRACT
Seven topics previously described in this column are revisited. The use of quantitative electroencephalography has been shown in a prospective study to be effective for predicting antidepressant treatment response. A novel antidepressant drug, agomelatine, has generated much controversy, and its development for the U.S. market was discontinued. A long awaited revised system for categorizing the safety of medications during pregnancy and lactation has finally been published by the Food and Drug Administration. Dextromethorphan/quinidine, eslicarbazine acetate, levomilnacipran, and esketamine are recent examples of drugs that were developed based on the complex concepts of chirality and stereochemistry. Lisdexamfetamine, a stimulant drug, failed to show benefit as an augmentation therapy for the treatment of depression. The combination drug naltrexone/bupropion was finally approved as a therapy for obesity, after its cardiovascular safety was confirmed in a prospective premarketing study. Further development of the glucocorticoid receptor antagonist drug mifepristone as a treatment for psychotic depression was stopped based on a large negative trial, but the drug continues to be investigated for other potential psychiatric indications. These examples illustrate how the field of psychopharmacology continues to evolve.

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Having written more than 100 columns for the Journal of Psychosocial Nursing and Mental Health Services during the past decade, I thought it would be of interest to look back in time and provide a follow up on some of the subjects I covered. I chose to revisit seven particular topics because of meaningful developments since I first wrote about them.

ELECTROENCEPHALOGRAPHY AND THE TREATMENT OF DEPRESSION
Since I wrote about the potential use of quantitative electroencephalography (QEEG) for predicting antidepressant treatment response in 2006 (Howland, 2006), a large prospective multicenter study investigating the predictive use of QEEG has been completed.

Leuchter, Cook, Gilmer, et al. (2009) examined the antidepressant treatment response (ATR) index as a predictor of differential response and remission to escitalopram (Lexapro®), bupropion (Wellbutrin®; Zyban®), or a combination of both medications in 375 study participants with major depression. All participants had a baseline QEEG study followed by 1 week of treatment with escitalopram, after which a second QEEG was performed, and the ATR index was calculated. Participants were randomized to continue escitalopram, switch to bupro-
pion, or receive the combination. Clinical response was assessed at 49 days of treatment. Accuracy of ATR in predicting response and remission was calculated. No significant differences were noted between response and remission rates in the three treatment groups. A single ATR threshold was useful for predicting differential response to either escitalopram or bupropion monotherapy. Participants with ATR values above the threshold were more than twice as likely to respond to escitalopram as those with low ATR values (68% response rate versus 28% response rate). Participants with ATR values below the threshold who were switched to bupropion also were twice as likely to respond to bupropion alone as those who remained on escitalopram (53% response versus 28% response). The ATR index did not provide a useful prediction of response to combination treatment.

In an additional analysis, Leuchter, Cook, Marangell, et al. (2009) examined the ATR index as a predictor of response to escitalopram and compared the ATR with other putative predictors of treatment outcome in 73 study participants who received escitalopram for 49 days. Response and remission rates were 52.1% and 38.4%, respectively. The ATR predicted both response and remission with 74% accuracy. Neither serum drug levels nor two genetic polymorphisms were significant predictors of treatment response or remission. Clinician prediction based on global impression of improvement at Day 7 did not predict outcome. The ATR index also predicted remission at 13 weeks as well as the speed of achieving sustained remission with escitalopram (Cook et al., 2013).

AGOMELATINE FOR THE TREATMENT OF DEPRESSION

I first described agomelatine in 2007 as a novel atypical antidepressant drug that was being actively investigated in pivotal studies, but had not yet been approved for use in Europe or the United States (Howland, 2007). Agomelatine was subsequently approved by the European Medicines Agency (EMA) in 2009 with the trade name Valdoxan. Its development in the United States, however, was stopped in October 2011 because the results of U.S. trials were disappointing (Howland, 2011). Approval of this drug by the EMA generated considerable controversy in Europe and Australia, mainly because of concerns about its limited effectiveness and issues surrounding conflicts of interest. The gist of this controversy can be read on the 1 Boring Old Man website (access http://1boringoldman.com/index.php/2012/01/24/its-about-time-4) as well as in a series of letters to the editor published in the January 21, 2012 issue of The Lancet, which included a letter I wrote (Howland, 2012a). In the midst of this controversy, I was also inaccurately accused by an anonymous blogger of “hiding” conflicts of interest of my own (Howland, 2013c).

In August 2014, the Prescription Medicines Code of Practice Authority (PMCPA; 2014) of The Association of the British Pharmaceutical Industry censured Servier (i.e., the European manufacturer of Valdoxan) for failing to disclose clinical trial results within an internationally agreed time frame. Servier breached several clauses of the PMCPA codes: (a) bringing discredit upon, and reducing confidence in, the pharmaceutical industry; (b) failing to maintain high standards; and (c) failing to meet the required time frame to disclose details of clinical trials.

CATEGORIZING THE SAFETY OF MEDICATIONS DURING PREGNANCY AND LACTATION

In 2009, I reviewed a revised pregnancy and lactation labeling system the FDA had proposed in May 2008 (Howland, 2009a). The FDA (2014) published its final rule on the revised system in December 2014. The final rule requires the use of three subsections in the labeling: pregnancy, lactation, and females and males of reproductive potential. The subsections must include a summary of the risks of using the drug during pregnancy and breastfeeding, a discussion of the data supporting the summary, and relevant information to help health care providers make prescribing and counseling decisions.

The pregnancy subsection provides information relevant to the use of the drug in pregnant women (e.g., dosing and potential risks to the developing fetus). This subsection also requires information about whether a registry exists that collects and maintains data on how pregnant women are affected by the drug. The lactation subsection provides information about using the drug while breastfeeding, such as the amount of drug in breast milk and potential effects on the child. The females and males of reproductive potential subsection includes information about pregnancy testing, contraception, and infertility as it relates to the drug.
The pregnancy and lactation subsections include three subheadings: risk summary, clinical considerations, and data. These subheadings provide more detailed information regarding human and animal data on the use of the drug and specific adverse reactions of concern for women who are pregnant or breastfeeding.

Along with publishing the final rule, the FDA issued a draft guidance for industry to help manufacturers comply with the new requirements. Final guidelines will not be issued until after the public comment period on the draft guidelines ends on February 2, 2015.

CHIRALITY AND STEROEOREMISTRY IN PSYCHOPHARMACOLOGY

I described the complex concept of chirality as it relates to psychopharmacological drug development in two columns in 2009 (Howland, 2009b,c). Stereoisomers are compounds that possess the same molecular and structural formula, but differ in their three-dimensional configuration. Chiral compounds have two mirror-image stereoisomer forms called enantiomers. Compounds that contain both mirror-image enantiomers in equal proportions are referred to as racemic mixtures or racemates.

New drugs continue to be developed based on their stereochemical properties. For example, in 2010, the proprietary drug combination dextromethorphan/quinidine (Nuedexa®) was approved for the treatment of pseudobulbar affect, a neurological condition characterized by involuntary uncontrollable crying and/or laughter (Anonymous, 2011). This drug is an interesting and unusual combination of two different stereoisomer drugs. Dextromethorphan (Robitussin®), the d-stereoisomer of the chiral racemate drug methorphan, is a cough suppressant at low doses and has dissociative and hallucinogenic effects at higher doses. Levomethorphan, the l-stereoisomer of methorphan, is an opioid analgesic drug. Quinidine (Quinindex®), a cardiovascular anti-arrhythmic drug, is a stereoisomer of quinine (Qualaquin®), which has anti-malarial, analgesic, and anti-inflammatory properties. Quinine has also been used to treat leg cramps, although the FDA warns against this use for safety reasons.

Three other recent examples of stereoisomer drugs are worth noting. First, eslicarbazepine acetate (Aptiom®; known as BIA 2-093) was approved in 2013 for treating epilepsy (Anonymous, 2014b). This acetate drug is an inactive prodrug that is converted to the pharmacologically active drug eslicarbazepine, which is the S-isomer of the chiral drug licarbazepine. Licarbazepine is an active metabolite of the anticonvulsant oxcarbazepine (Trileptal®). Oxcarbazepine is a structural derivative of carbamazepine (Tegretol®; Equetro®), which is approved for the treatment of bipolar disorder. BIA 2-093 was ineffective compared to placebo for the acute treatment of mania in two unpublished studies. Results from these studies are posted on the ClinicalTrials.gov website (NCT01824602; NCT01822678). Second, levomilnacipran (Fetzima®), approved in 2013 for the treatment of major depression (Anonymous, 2013), is the more pharmacologically active enantiomer of the chiral drug milnacipran (Savella®), an approved treatment for fibromyalgia. Finally, esketamine is the S-enantiomer of the chiral drug ketamine (Ketalar®), an injectable anesthetic drug that has been studied for treating depression (Howland, 2013a). An intranasal esketamine formulation is being investigated as a rapid treatment for depressed patients at imminent risk of suicide and in treatment-resistant depression (NCT02133001; NCT01998959 on the ClinicalTrials.gov website).

STIMULANT DRUGS FOR THE TREATMENT OF DEPRESSION

In a previous column, I described the use of various dopaminergic and stimulant drugs, including lisdexamfetamine (Vyvanse®), for the treatment of depression (Howland, 2012b). Since that column was published, two Phase 3, multicenter, randomized, double-blind, placebo-controlled, efficacy and safety studies of lisdexamfetamine augmentation have been completed. In these two studies, lisdexamfetamine or placebo was used in combination with an antidepressant agent in depressed individuals with inadequate response to prospective treatment with an initial antidepressant drug alone. The study blinds were broken in February 2014. Both studies failed to demonstrate significant benefit for lisdexamfetamine augmentation compared to placebo. These studies have not been published, but results are available on the ClinicalTrials.gov website (NCT01436149; NCT01436162).

DRUG THERAPIES FOR OBESITY

In a column describing several new weight loss products (Howland, 2013d), the fixed-dose combination of the opioid receptor antagonist drug naltrexone (ReVia®) and the antidepressant and smoking cessation drug bupropion had not yet been approved. An FDA advisory group recommended approval of naltrexone/bupropion, with the stipulation that a cardiovascular study be conducted after approval, but the FDA declined to grant final marketing approval until the cardiovascular study was completed. An interim analysis (announced in November 2013) of the cardiovascular outcomes trial in overweight and obese adults with cardiovascular risk factors found that naltrexone/bupropion did not increase the risk of major adverse cardiovascular events (Anonymous, 2014a). The cardiovascular study is ongoing, but the combination product (Contrave®) was approved in September 2014 based on the favorable find-
ings from the interim analysis (Anonymous, 2014a).

MIFEPRISTONE FOR THE TREATMENT OF PSYCHOTIC DEPRESSION

In 2013, I described the pharmacology of the glucocorticoid receptor antagonist drug mifepristone (RU-486; Mifepriva®; Koryln®) and its potential use for the treatment of psychotic depression (Howland, 2013b). In May 2014, the manufacturer (Corcept) announced that it had discontinued a Phase 3 study of mifepristone and was stopping further development of this drug for psychotic depression. This study was not stopped for safety reasons, but an interim data analysis from the first 226 patients enrolled in the study (NCT00637494 on the ClinicalTrials.gov website) showed that the drug had failed to reach statistical significance on its primary endpoint (i.e., a rapid and sustained reduction in psychotic symptoms). The independent data monitoring committee advised Corcept that continuing the study to its full enrollment of 450 patients would be unlikely to generate a statistically significant result. Mifepristone is still being investigated in clinical studies for posttraumatic stress disorder and alcohol dependence.

CONCLUSION

“What’s past is prologue” (Act 2, Scene 1) wrote William Shakespeare in The Tempest, and so it is with psychopharmacology. The field is ever evolving, from what we thought we knew in the past, to what we now know today, and on to what we will learn in the future.

REFERENCES


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