

CNS Drug Development: Lessons from the Development of Ondansetron, Aprepitant, Ramelteon, Varenicline, Lorcaserin, and Suvorexant. Part I

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This column is the first in a two-part series exploring lessons for psychiatric drug development that can be learned from the development of six central nervous system drugs with novel mechanisms of action over the past 25 years. Part 1 presents a brief overview of the neuroscience that supported the development of each drug, including the rationale for selecting a) the target, which in each case was a receptor for a specific neurotransmitter system, and b) the indication, which was based on an understanding of the role that target played in a specific neural circuit in the brain. The neurotransmitter systems on which the development of these agents were based included serotonin for ondansetron and lorcaserin, dopamine for varenicline, substance P (or neurokinin) for aprepitant, melatonin for ramelteon, and orexin for suvorexant. The indications were chemotherapy-induced nausea and vomiting for ondansetron and aprepitant, smoking cessation for varenicline, weight loss for lorcaserin, and insomnia for suvorexant and ramelteon. (*Journal of Psychiatric Practice* 2014;20:460–465)

KEY WORDS: ondansetron, aprepitant, ramelteon, varenicline, lorcaserin, suvorexant, central nervous system, novel mechanism of action, drug development, neurotransmitters, dopamine, melatonin, neurokinin, orexin, serotonin, substance P

This column is an extension of themes that I have discussed in several earlier columns.¹ It concerns the crisis in psychiatric drug development and what can be learned from the development of six central nervous system (CNS) drugs with novel mechanisms of action. This drug development crisis is reflected in two facts. First, most major pharmaceutical companies have stopped developing psychiatric drugs. Second, no mechanistically new antipsychotic and antidepressant drugs have been developed during the past 50 years, with the possible exception of bupropion.^{2–4} That is not to say that no “new” mole-

cules have been developed in the past 50 years, but rather that all of the “new” molecules that were developed involved variations on the mechanisms of chlorpromazine and imipramine. That is also not to say that none of these developments was important. The most notable advances have involved the development of much safer antidepressants. Whereas tricyclic antidepressants (e.g., imipramine) could routinely kill a patient if a 2-week supply were taken all at once, such an occurrence is virtually impossible with selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). Smaller advances have been made in the development of newer antipsychotics, with relatively modest gains despite a large expenditure of time and money.⁵ Despite this sad state of affairs with regard to antidepressants and antipsychotics, at least six mechanistically new central nervous system (CNS) drugs have been developed in the past 25 years (Table 1). This two-part series will focus on the lessons that can be learned from the development of these drugs that may be potentially applicable to the development of mechanistically novel antidepressants and antipsychotics.

In this first part of the series, I will present a brief review of the discovery and development of each of these drugs in the order in which they were approved by the U.S. Food and Drug Administration (FDA).

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Table 1. Six central nervous system drugs with novel mechanisms of action developed in the past 25 years

<i>Generic name</i>	<i>Brand name</i>	<i>Originator</i>	<i>Approval date</i>	<i>Latest PI revision</i>	<i>Indication(s)</i>	<i>Mechanism</i>	<i>Generic available</i>
Ondansetron	Zofran	Glaxo	1/4/1991	9/18/2014	Chemotherapy-induced nausea and vomiting (CINV)	Serotonin 5-HT ₃ receptor antagonism	7/2/2010
Aprepitant	Emend	Merck	3/27/2003	8/12/2014	CINV	Neurokinin (substance P)-1 receptor antagonism	7/24/2012
Ramelteon	Rozerem	Takeda	7/22/2005	3/1/2012	Insomnia ^b	Melatonin (MT ₁ , MT ₂) receptor agonism	7/26/2013
Varenicline	Chantix	Pfizer	5/10/2006	10/15/2014	Smoking cessation	Acetylcholine nicotinic receptor alpha-4 beta-2 partial agonism	No
Lorcaserin	Belviq	Arena ^a	6/27/2012	6/27/2012	Weight loss	5-HT _{2C} agonism	No
Suvorexant	Belsomra	Merck	8/13/2014	N/A	Insomnia ^c	Dual orexin 1 and 2 receptor antagonism	No

PI: package insert

^aMarketed by Eisai ^bDifficulty with sleep onset ^cDifficulties with sleep onset and/or sleep maintenance

Ondansetron

This drug is approved for the treatment of chemotherapy-induced nausea and vomiting (CINV). The initial steps in the scientific exploration that led to the discovery and development of ondansetron occurred in 1935 when Vittorio Erspamer in Italy isolated from enterochromaffin cells a substance he called enteramine, because it caused intestinal preparations to contract.⁶ In 1948, Maurice Rapport and colleagues in the United States isolated a substance from blood that could cause vasoconstriction and hence named it “serum tonic factor” or “serotonin.”⁷ By 1952, it was recognized that these two substances were the same chemical. The name serotonin (which is chemically 5-hydroxytryptamine, abbreviated 5-HT) was widely adopted. By 1953, Twarog and Page had isolated it from the brain.⁸ By the early 1960s, Falck and Hillarp had developed a fluorescent method of visualizing serotonin in tissue, which allowed for the identification of the cell bodies for serotonin in the brain and their projections to other regions.⁹ In the brain, serotonin neurons are located principally in the dorsal and lateral raphe

nuclei in the brainstem, but their projections innervate many regions in the brain and project down the spinal cord. Of particular relevance to the discovery of ondansetron was the finding that the area postrema in the brainstem was also densely innervated by 5-HT fibers from the raphe.

The next major advance was the identification of the various receptors for serotonin, followed by the ability to map these receptors in brain regions innervated by serotonin projections. Of the more than 17 different subtypes of serotonin receptors identified to date, the 5-HT₃ receptor (5-HT is by convention used to designate these receptors rather than an abbreviation for serotonin) was found to be densely located in the area postrema. Basic research determined that serotonin released in this area produced nausea and vomiting.

The isolation of the gene for the 5-HT₃ receptor allowed researchers to determine its structure and function. It is the only 5-HT receptor that is an ion channel rather than a G protein-coupled receptor. Based on its structure, medicinal chemists could develop molecules that would bind to this channel and block the effect of serotonin on it. From those

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molecules, ondansetron was selected based on its favorable “drug-ability” characteristics for clinical development.

Harking back to the work of Vittorio Erspamer, emetogenic cancer chemotherapeutic agents cause the release of serotonin from the enterochromaffin cells of the small intestine and may also stimulate vagal afferents (via 5-HT₃ receptors) to initiate the vomiting reflex. That was the final critical piece of information needed to decide on a development plan for ondansetron with the goal of demonstrating whether it could treat CINV. That plan was successful and led to its FDA approval for this indication.

GlaxoSmithKline, which developed ondansetron, also investigated its use in a number of other neuropsychiatric conditions, including senile dementia of the Alzheimer’s type, Parkinson’s disease, schizophrenia, and anxiety and depressive disorders. These development efforts were unsuccessful, which is why the drug has only one indication.

Aprepitant

This drug is also approved for CINV but its development took a somewhat more circuitous route than that of ondansetron. Substance P was identified as a neurotransmitter in 1931.¹⁰ Initially substance P was thought to be important for the mediation of pain. Hence, a number of companies developed drugs and tested them for this indication to no avail.

Substance P is also known as neurokinin (NK). Three receptors for this neurotransmitter have been identified: NK-1, NK-2, and NK-3. Neuroanatomical mapping studies showed that neurokinin heavily innervates the nucleus of the dorsal vagus complex in the brainstem via the NK-1 receptor subtype. Studies have shown that the nucleus of the dorsal vagus complex also contributes substantially to nausea and vomiting. Armed with this information, Merck initiated a development program to test the effectiveness of aprepitant in CINV, and that program led to FDA approval of the drug for this indication.

Neurokinin is also found in regions of the brain that are important in the regulation of emotion.¹¹ For this reason, aprepitant was tested as an antidepressant. The initial proof of concept study was robustly positive. The results along with the rationale for the study were published in the journal *Science* in 1998 and generated considerable enthusiasm.¹² However, subsequent studies of aprepitant were negative.¹³

Merck also tested another highly selective NK-1 antagonist, L-759274, with positive results in one clinical trial, but then abandoned work on this mechanism of action as a potential treatment for major depression.¹⁴

However, interest in this potential mechanism of action remains, and two newer highly selective NK-1 antagonists have recently been tested in moderate to severe major depression, with positive results for one of the agents but only at doses that produce almost 100% occupancy of the NK-1 receptor in the frontal cortex.¹⁵ Parenthetically, this degree of receptor occupancy is higher than that needed or tolerated in terms of 5-HT transporter occupancy for antidepressant efficacy for SSRIs and SNRIs and D-2 receptor occupancy for antipsychotic efficacy without causing extrapyramidal side effects. Thus, these results suggest the need for more work to understand this system and its potential relevance to the treatment of major depressive disorder.

Ramelteon

Since antiquity, the pineal gland has been viewed as providing a connection between the physical and spiritual realms.¹⁶ Descartes proposed that it controlled communications between the physical body and its surroundings, including emotions. In 1958, interest in the association between the pineal gland and psychiatric functioning was rekindled by the discovery of melatonin.¹⁶ Melatonin was subsequently found to innervate the suprachiasmatic nucleus (SCN) via two G protein-coupled receptors, MT₁ and MT₂.¹⁷ Both receptors are highly expressed in the SCN, which is a primary mammalian circadian pacemaker. Melatonin in the SCN is responsible for sleep initiation via actions on MT₁ and MT₂ receptors.

Based on this biological knowledge, drug discovery aimed at producing agonists at MT₁ and MT₂ receptors led to the development of ramelteon. Clinical trials with this drug led to its approval by the FDA for the treatment of insomnia characterized by difficulty with sleep onset.

Varenicline

Varenicline, a partial agonist of the acetylcholine nicotinic receptor alpha-4 beta-2, is approved by the FDA for smoking cessation. Acetylcholine was identified as a neurotransmitter in 1921,¹⁸ and two sub-

types of acetylcholine receptors, muscarinic and nicotinic, were identified based on the substances that bind to them.

In contrast to ondansetron and aprepitant, the discovery of varenicline formed part of an older tradition in the pharmaceutical industry—the development of a new molecular entity based on a natural substance found in a plant extract. The *Cytisus* plant was used as a smoking substitute during World War II and that use continued in eastern Europe when cigarettes were in short supply.¹⁹ Cytisine was extracted from the plant and found to be the active ingredient. Varenicline was the result of medicinal chemistry work by Pfizer to find a patentable new molecular entity that was more effective and better tolerated.²⁰

Concurrent with this traditional approach, advances in neuroscience were providing an explanation for the mechanism of action. That involved mapping cholinergic pathways in the brain and finding innervation of dopamine (DA) neurons of the ventral tegmentum area (VTA). Those DA neurons in turn were found to innervate the nucleus accumbens, commonly known as the “pleasure center of the brain,” a region implicated in many forms of drug (e.g., nicotine from smoking) and even behavioral (e.g., gambling) addictions.^{21,22}

Smoking was found to stimulate the firing of DA neurons in the VTA via the alpha-4 beta-2 nicotinic receptor located on the DA neuron and hence the release of DA in the nucleus accumbens. In an effort to develop an animal model for smoking, it was found that rats could be trained to smoke; however, that was not possible in rats that were genetically deficient in the alpha-4 beta-2 receptor (i.e., genetic knockout animals).²³ As a long-lived partial agonist, varenicline antagonizes the rewarding effect of nicotine without producing nicotine withdrawal. In essence, varenicline produces a pharmacologic analog in man of the alpha-4 beta-2 knockout rat. Parenthetically, bupropion had already been approved as an aid for smoking cessation and also works through action on the nucleus accumbens.

Armed with this research and further supported by the success of bupropion, Pfizer conducted trials of varenicline as an aid in smoking cessation. Those trials were successful and resulted in the drug’s approval for this indication. Parenthetically, Pfizer excluded subjects with active psychiatric illness from their smoking cessation trials. However, the incidence of smoking is disproportionately high in indi-

viduals with psychiatric illness, particularly in those with schizophrenia and affective disorders compared to individuals without these illnesses. Thus, it is not surprising that persons with these illnesses would use varenicline. Since these illnesses are likely due in part to dysregulation of these systems, it is possible that the reports of increased suicidal ideation and other behavioral abnormalities in some individuals with these illnesses when they use varenicline may be due to an interaction between the pharmacology of the drug and the biology underlying their illnesses. While that is intriguing, further discussion of that possibility is beyond the scope of this column.

Lorcaserin

Lorcaserin was the first drug in a decade to receive FDA approval as an aid to weight loss and it had a new mechanism of action. It is a 5-HT_{2C} agonist.²⁴ The science underlying its development parallels that of ondansetron so that will not be repeated here. The 5-HT_{2C} receptor is heavily—but not exclusively—expressed in the satiety centers in the hypothalamus. Moreover, genetically knocking out the 5-HT_{2C} receptor in rats produces an animal model of morbid obesity. Finally, drugs that have high affinity for and block the 5-HT_{2C} receptor centrally cause weight gain and the metabolic syndrome.^{25–27}

Armed with this information, drug developers with Arena Pharmaceuticals searched for new molecular entities that were 5-HT_{2C} agonists and capable of crossing the blood;brain barrier. The result was lorcaserin, which went into clinical trials as an aid to weight loss and received approval based on those studies.

Suvorexant

This drug is a dual orexin 1 and 2 receptor antagonist and is the first CNS drug to trace its development directly from a genetic finding. It also went from discovery to approval in approximately 8 years, which is about half the time needed for most CNS drug approvals.

Briefly, the suvorexant story began in 1998 when two independent research groups discovered the neurotransmitter orexin (also known as hypocretin).^{28,29} This discovery was the result of searching fragments of human DNA for genes for previously unknown G protein-coupled receptors (so

called “orphan” receptors) and then using them to identify the previously unknown neurotransmitter.³⁰

Following its discovery, orexin was found to be produced by a relatively small number (i.e., approximately 100,000) of excitatory neurons localized in the lateral hypothalamus.³¹ Genetic variants in orexin receptors were then found to be responsible for canine narcolepsy,^{32,33} whereas, loss of orexin neurons was found to be responsible for human narcolepsy.³⁴ Based on these findings and others, the circadian firing of orexin neurons was discovered to be critical to maintaining arousal and stability of the wake state in the mammalian brain and to be highly conserved across a number of mammalian species from rodents to dogs to primates to man.

Armed with this knowledge, Merck drug discoverers sought new molecular entities capable of blocking these receptors.³⁵ Suvorexant was the result of that search and entered into clinical development in 2006. It received FDA approval 8 years later for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance.

Conclusion

This column has presented a brief history of the background that led to the development of six CNS drugs with novel mechanisms of action. Part 2 of this series will discuss similarities in the development of these drugs and lessons that can be learned from their development to aid in the search for and development of novel drugs for the treatment of psychiatric disorders.

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