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THE MANAGEMENT OF NEURODEGENERATIVE SYMPTOMS IN HUNTINGTON'S DISEASE

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Huntington's disease (HD) is a genetically programmed disease in which neuronal degeneration occurs in certain areas of the brain. The degeneration of neurons leads to uncoordinated, jerky movements of the body called chorea, loss of intellectual faculties, and uncharacteristic changes in mood and behavior. These complications eventually lead to a deteriorated quality of life and reduced life expectancy. HD was first documented in 1872 by the American physician George Huntington. The disease affects about 1 per 10,000 people of European ancestry with a slightly lower incidence rate in people of Chinese, Japanese, or African descent. Individuals with the adult-onset form of HD usually live 15 to 20 years after signs and symptoms appear. The adult-onset form of HD develops anywhere between 30-50 years of age. Early-onset (juvenile) HD tends to be more severe and individuals usually only live 10 to 15 years after signs and symptoms first present. Juvenile HD usually develops before the age of 20 and accounts for 7-16% of all HD cases.¹ This article will review the signs and symptoms, genetics, mechanism, and diagnosis of the disease to help provide an insight on how specific drugs work. The main focus will be on currently approved and investigational treatment options for the management of HD.

DISEASE BACKGROUND

HD can present through a variety of signs and symptoms. In adult-onset HD, initial symptoms include chorea, unsteady gait, slurred speech, lack of coordination, sleep disturbances, and chewing and swallowing difficulty leading to weight loss and malnutrition. Very slow movements and stiffness can sometimes occur as the disease progresses. Many people with the juvenile akinetic rigid variant of HD (Westphal variant of HD) suffer from seizures (30-50%), bradykinesia, and Parkinson-like symptoms.² Cognitive deficits, including loss of executive function and memory, are seen frequently with disease progression. Psychiatric symptoms such as aggression, anxiety, depression, egocentrism, and compulsiveness are frequent in HD patients. Worsening of addictions to alcohol and gambling, and hypersexuality have all been reported.³

GENETIC BASIS OF DISEASE

The Huntingtin gene (HTT) is located on the short arm of chromosome 4 and it contains a sequence of trinucleotide repeats, CAG (cytosine, adenine, guanine), on its 5' end. Repeats of CAG are often called polyglutamine or polyQ since the amino acid glutamine is derived from this trinucleotide sequence. The average human typically has 26 or less

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repeats of CAG within the HTT gene. In people with HD, the CAG segment is repeated 36 to more than 120 times. Production of mutant Huntingtin gene (mHTT) results in neuronal decay in certain areas of the brain. A segment count of 27-35 repeats is classified as “intermediate” with the patient not likely to be symptomatic but can still pass on the autosomal dominant gene to successive generations. A segment count of 36-39 repeats is classified as “reduced penetrance” in which a much later onset and slower progression of symptoms occurs compared with typical HD. Many of these patients may die of other causes before any HD symptoms are manifested. Repeats of >39 glutamines is considered to be “full penetrance” and a patient will be affected by HD. The length of repeats correlates inversely with the age of onset and the rate of progression of symptoms.⁴

Each offspring of an affected individual has a 50% chance of inheriting the mutant allele because HD is inherited autosomal dominantly. All “intermediate” and “reduced penetrance” carriers have a chance of passing down fully penetrant HD. Maternally inherited alleles are generally of the same repeat length but paternally inherited alleles are generally of larger repeat length. In 1-3% of affected individuals, no family history can be found, suggesting a *de novo* mutation as the culprit for this rare phenomenon.

The function of Huntingtin (HTT) is unclear in humans but in mice models it plays a vital role in upregulating the expression of Brain Derived Neurotrophic Factor (BDNF) by acting as a transcription factor. BDNF is a protein which protects neurons and regulates neurogenesis; however, production of BDNF is suppressed in mHTT models, leading to progressive atrophy of certain areas of the brain. The area of the brain with the most spiny neuronal loss is the striatum, with the frontal and temporal cortices affected to a lesser degree.⁵

DIAGNOSIS

In diagnosing HD, psychological and physical examinations are used to determine symptoms initially. CT or MRI scans are used to determine changes in brain structure if HD is suspected and a definite diagnosis can be given with a blood test from the suspected individual testing for the amount of CAG repeats on each of the HTT alleles. If the results are unclear, the parents of the suspected individ-

ual can have blood tests done to help confirm the diagnosis.

TREATMENT OPTIONS

Alleviating symptoms is the primary goal of treatment and the focus of current treatment options for this disease. The drugs used to treat movement disorders of HD will be discussed first, followed by the treatment of psychiatric and behavioral symptoms. Numerous investigational agents being researched as possible breakthrough treatment options for HD will be discussed later.

Tetrabenazine (Xenazine[®]) is currently the only FDA approved drug for the treatment of chorea in HD and it is the first drug of any kind approved for treatment of any symptoms associated with HD in the US. In HD patients, there is an excessive amount of dopamine located in nerve synapses within the brain causing over excitation and allowing chorea symptoms to be unmasked over time. Tetrabenazine (TBZ) acts by decreasing the amount of dopamine at these synapses, thus minimizing symptoms of chorea. It selectively binds to the presynaptic vesicular monoamine transporters (VMAT2) blocking reuptake of dopamine, norepinephrine, and serotonin from the cytosol into presynaptic vesicles. This process secondarily decreases monoamine and serotonin levels by increasing degradation of these molecules. The process of VMAT binding and monoamine depletion by TBZ is reversible, lasts hours, and is not modified by chronic treatment. TBZ also antagonizes postsynaptic dopamine receptors. In a double-blind, placebo-controlled study of 84 patients with HD, TBZ was found to significantly reduce chorea and provide a significant benefit on ratings of clinical global improvement.⁶ In an evidence-based review, Bonelli and Wenning reported that TBZ appeared effective in reducing chorea in 7 out of 8 small level-II double-blind studies. In this review, randomized controlled trials represent level-I studies if the following are present: a minimum of 2 weeks treatment period on active drug, a minimum of 10 HD patients on active drug completing the study, and a full paper citation. If a randomized controlled trial did not meet these criteria then it was classified as a level-II study along with non-randomized or observational controlled trials. Level-III was assigned to uncontrolled case series, i.e. retrospective reports and open label trials.⁷ Frank et al. evaluated chorea symptoms in 30 patients after abrupt TBZ with-

drawal demonstrating an increase of chorea scores of 2.3 units from days 1 to 3 after withdrawal compared to placebo. This study also demonstrated that sudden withdrawal of TBZ up to 150mg appears safe.⁸ Insomnia, depression, drowsiness, restlessness, dysphagia, and nausea have all been reported as possible side effects of TBZ. In a single-blind, cross-over, level-II study by Giminez-Roldan and Mateo, severe depression occurred in 3 of 11 HD patients on TBZ and 1 led to a suicide attempt.⁹ Decreasing the amount of dopamine at different neuronal synapses can cause depression and suicidal ideation in some individuals; therefore, the FDA required a Risk Evaluation and Mitigation Strategy (REMS) to help ensure that the benefits outweigh the risks. A medication guide is required to be given to patients upon dispensing as a result of this REMS. TBZ was granted orphan drug designation by the FDA since HD affects less than 200,000 individuals in the US.¹⁰

Haloperidol (Haldol[®]), a widely established antipsychotic drug, can be effective in ameliorating HD-related chorea as demonstrated in 3 level II and 3 level III studies.⁷ Barr, et al. found low-dose haloperidol (< 10 mg/day) effective in reducing chorea in an open pilot study with little added clinical benefit at doses > 10 mg/day.¹¹ Fluphenazine (Prolixin[®]), another typical antipsychotic, has shown effectiveness in reducing chorea in a small level II trial, confirmed by level-III data and a case report.⁷ Haloperidol and fluphenazine work by blocking postsynaptic D2 receptors in the mesolimbic system and increase dopamine turnover by blocking the D2 somatodendritic autoreceptor. After about 12 weeks, depolarization of the dopamine tract occurs and there is a significant decrease in dopamine neurotransmission.¹² Both of these typical antipsychotic are known to cause extrapyramidal symptoms (EPS) so close monitoring is necessary.

Atypical antipsychotics have also been evaluated for treating movement disorders associated with HD. Olanzapine (Zyprexa[®]) improved behavioral subscores with low doses (5mg/day) in 2 level III studies, but higher doses (up to 30mg/day) significantly reduced not only chorea, but also orolingual dysfunction, finger dexterity, and gait in an additional level III study. In a series of case reports, Risperidone (Risperdal[®]) appears to be useful for the treatment of HD associated psychosis and chorea. Quetiapine (Seroquel[®]) and ziprasidone (Geodon[®]) have both been shown to increase motor function of the Unified

HD Rating Scale (UHDRS) in other case reports. Clozapine (Clozaril[®]) has been the best documented drug but has shown the least efficacy and the most severe SE's including leukopenia.⁷ The atypical antipsychotics generally cause less EPS than the typical antipsychotics due to less D2 receptor antagonism and more 5-HT2 receptor blockade.¹²

In the last decade, glutamate has been postulated to play an important role in HD, in part because intrastriatal injections of glutamate agonists (especially NMDA receptor agonists) produce the symptoms of HD.¹³ In transgenic HD models, glial glutamate reuptake transporters are decreased which ultimately results in increased synaptic glutamate.¹⁴ Some evidence suggests NMDA receptors are more sensitive to intracellular Ca²⁺ influx and excitotoxicity when mHTT protein interacts with them.¹⁵ Amantadine (Symmetrel[®]) and memantine (Namenda[®]) both have inconclusive evidence regarding their usefulness in HD. Amantadine has not established a clear mechanism of action but some suggest it is similar to memantine which acts as a low to moderate noncompetitive antagonist of NMDA receptors. Blockade of these receptors leads to a decreased excitatory state, in turn, decreasing Ca²⁺ influx and preventing further nerve damage to the brain.¹² Vernagen-Metman, et al. published a high-quality level-I study demonstrating amantadine (400 mg/day) lowered chorea scores, with a median reduction in extremity chorea at rest of 36% for all 22 evaluable patients.¹⁶ In contrast, a high-quality, level-I randomized, placebo-controlled, cross-over trial conducted by O'Suilleabhain and Dewey demonstrated that 2 weeks of treatment with amantadine (300 mg/day) did not have any effect on chorea in HD patients.¹⁷ Multiple lower level studies and case reports confirmed this. Amantadine may increase irritability and aggressiveness in HD patients, thus it is unclear what role this drug may play in the treatment of HD.⁷ Memantine, which is used frequently to diminish dementia symptoms in Alzheimer's patients, might play a role in HD. Memantine can retard HD progression by decreasing motor function decline. Beister, et al. conducted a two-year study with memantine (up to 30 mg/day) in 27 HD patients recruited from two different clinics. The results suggested that the placebo group had a 21.2% decrease in motor function over 2 years compared to 4.3% in the memantine group, however further research is needed.¹⁸

Myoclonus is a rare feature of HD and antidopa-

Table 1. Summary of Clinical Trials for the Management of Neurodegenerative Symptoms in Huntington's Disease

AUTHORS	NUMBER STUDIED	ACTIVE DRUG: DOSE	PURPOSE	RESULTS
Huntington Study Group (2006) ⁶	TBZ, n=54 Placebo, n=30	Tetrabenazine: up to 100 mg/day for 12 weeks	Antichorea	5.0 unit decrease in chorea severity with active group compared to 1.5 unit decrease with placebo (p<0.0001)
Frank, et al. (2008) ⁸	Withdrawal (W) of TBZ, n=12 Partial Withdrawal (PW), n=12 No Withdrawal (NW), n=6	Tetrabenazine: withdrawal of TBZ from patients on stable therapy for at least 2 months	Antichorea	Adjusted mean chorea scores for W group increased by 5.3 units from day 1 to 3, vs. those in the combined PW and NW groups increased by 3.0 units (p=0.0773).
Gimenez, et al. (1989) ⁹	TBZ → Haloperidol, n=11 (cross-over)	Tetrabenazine: varied dose	Antichorea	Though improvement in chorea scores over baseline was greater with TBZ, 46.3 (±23.4), vs. haloperidol, 28.6 (±47.7), the difference did not reach statistical significance.
Barr, et al. (1988) ¹¹	Haloperidol, n=10 Placebo, n=10	Haloperidol: 1 to 40 mg/day	Antichorea	Significant improvement of abnormal movements, >30% from baseline, occurred at concentrations of 2-5ng/ml, corresponded to doses of 1.5 to 10mg/day. Further improvement at serum concentrations above this range was minimal.
Verhagen Metman, et al. (2002) ¹⁶	Placebo → Amantadine, n=12 (cross-over) Amantadine → Placebo, n=12 (cross-over)	Amantadine: 400 mg/day for 2 weeks	Antichorea	Chorea scores lower with amantadine (usually 400 mg/d) vs. placebo, median reduction in extremity chorea at rest = 36% (p=0.04) for all 22 evaluable patients and = 56% in 10 individuals with highest plasma drug levels. Improvement correlated with plasma amantadine concentrations (p=0.01) but not CAG repeat length.
O'Suilleabhain, et al. (2003) ¹⁷	Placebo → Amantadine, n=14 (cross-over) Amantadine → Placebo, n=11 (cross-over)	Amantadine: 300 mg/day for 2 weeks	Antichorea	Chorea was not significantly affected by amantadine therapy. The chorea score was 9.6 (±3.1) at baseline and 9.7 (±3.7) on amantadine. 95% confidence interval was -1.43 to 1.0. Despite this, 19 subjects felt improved during the amantadine phase vs. 6 subjects in the placebo phase (p=.006) and the quality of life was better (p<.001).
Beister, et al. (2004) ¹⁸	Memantine, n=24 Placebo, number not reported	Memantine: up to 30 mg/day for 2 years	Improved Motor Function	Memantine treatment of HD may be useful to retard progression of the disorder
Saft, et al. (2006) ¹⁹	Valproic acid, n=8	Valproic acid: 300 to 2700 mg/day	Improved Myoclonic Hyperkinesia	In 7 patients myoclonus and UHDRS motor score improved in a dose dependent manner. Initial mean UHDRS motor score = 73.1 (± 11.9), after treatment mean UHDRS motor score = 60.2 (± 12.8) (p=0.042). 3 patients had antidepressant medication reduced.
Puri, et al. (2005) ²⁹	Ethyl-EPA, n=67 Placebo, n=68	Ethyl-EPA (purity > 95%): 2 gm/day for 12 months	Improved Motor Function	Ethyl-EPA had no benefit in the intent-to-treat cohort of patients with HD (p<0.05); exploratory analysis: significantly higher number of patients in per protocol cohort showed stable or improved motor function (p=0.06).

minergic medications are not typically effective for this problem. Myoclonus is normally associated with juvenile onset HD but this is not always the case. Numerous studies have shown the beneficial effect of valproic acid (Depakote®) on reducing myoclonus but not in reducing involuntary movements in choreatic hyperkinesias. Saft, et al. conducted a case-series that investigated over 600 people with HD. Eight of these patients had myoclonus as the main clinical symptom. Patients were scored by Unified Huntington's Disease Rating Scale (UHDRS) motor scores before and after treatment with valproic acid. Seven of the 8 patients had remarkable improvements in their motor function scores. An additional mood-stabilizing effect was observed in 5 cases and the 1 patient who did not show improvement was taking a daily dose of only 300 mg of valproate. All other patients were taking valproic acid 900-2700mg/day. Furthermore, mobility and manual dexterity were remarkably improved in these patients. Valproic acid's ability to increase GABA levels in the brain may explain its effectiveness in treating myoclonus which has been speculated to be caused by GABA deficiency.¹⁹ Valproic acid may be a plausible option for use in myoclonic hyperkinesia-dominant HD with the validation of future studies.

Approximately 80% of patients with HD suffer from some level of dystonia. Less commonly, patients suffer from severe functional impairment in which therapeutic intervention is required. In some individuals, chorea symptoms begin to lessen as the disease progresses and more functional capacity is lost. Sustained, involuntary torsion, called dystonia, begins to dominate as the primary motor dysfunction in these people.²⁰ Typical pharmacological treatment options for dystonia include anticholinergics, benzodiazepines, baclofen, dopaminergic agents, dopamine-depleting agents (rarely used), and botulism toxin injections.

Depression is the most frequent psychiatric symptom associated with HD and it normally starts as an isolated symptom. Beneficial results from case reports in HD patients have been reported for amitriptyline (Elavil®), imipramine (Tofranil®), fluoxetine (Prozac®), phenelzine (Nardil®), isocarboxazid (Marplan®), amoxapine, and mirtazapine (Remeron®). Psychosis is another symptom seen in approximately 3 to 12% of HD patients. This symptom ranges from nonspecific paranoia to presenta-

tions similar to schizophrenia.⁷ A case study conducted by Erdemoglu and Boratav demonstrated that risperidone (Risperdal®) offers clinical improvement for patients affected by psychosis.²¹

Frontal lobe dysfunction can cause increased irritability, lack of control, and aggression in some HD patients. Haloperidol was useful in treating irritability, depression, and aggressive outbursts in a double-blind, crossover level-II study. Olanzapine also showed a significant improvement in the UHDRS psychiatric subscores of depression, obsessions, irritability, and anxiety in 2 small level-III studies.⁷

According to DSM-III-R criteria of sexual disorders, 82% of HD patients experience one or more of these problems. Some patients may exhibit hypersexuality but sexual hypoactivity is more common. Two case reports show that leuprolide (Eligard®) and medroxyprogesterone (Provera®, Amen®) have been successful in the treatment of hypersexuality.⁷ Both of these agents act by decreasing the body's natural release of GnRH from the pituitary resulting in reduced steroidogenesis.¹²

Dementia is one of the three cardinal clinical features of HD and its prevalence depends on the clinical stage of the disease. It often subtly affects those who are asymptomatic gene-carriers of HD. Choline esterase inhibitors have been mostly ineffective in level-III trials and 1 case report, but galantamine (Razadyne®) has shown some promising results in multiple studies.⁷ Galantamine's ability to modulate the nicotinic acetylcholine receptors (nAChRs) via allosteric potentiation possibly contributes to its neuroprotective properties. Park, et al. conducted a study showing reduced neurological deficits and decreased mean striatal lesion volume in the galantamine treatment group compared to placebo.²² A possible reason for this might be from the allosteric potentiation of nAChRs leading to an up-regulation of bcl-2, an anti-apoptotic protein, causing suppression of apoptosis.²³ Galantamine exerts anti-oxidative effects by reducing oxidative damage, and restoring mitochondria membrane potential.²⁴ It is also a reversible inhibitor of acetylcholinesterase (AChE) thus decreasing the breakdown of acetylcholine.¹² Galantamine seems to offer hope for HD patients although evidence is limited.

Unsaturated fatty acids and minocycline (Minocin®, Solodyn®) have provided mild cognitive improvement in a few open label trials.⁷ Minocycline has been studied numerous times as a possible neuroprotective agent for use in HD and other

Table 2. Summary of Animal Studies for the Management of Neurodegenerative Symptoms in Huntington's Disease

AUTHORS	ACTIVE DRUG: DOSE	PURPOSE	RESULTS
Thomas, et al. (2008) ³²	HDACi 4b: 150 mg/kg/d for 67 days	Improved Motor Function	Brain weight significantly greater compared to placebo-treated mice (407.3 mg vs. 345.4 mg; $p=0.045$). Significant differences in motor performance
Park, et al. (2008) ²²	Galantamine: 1 mg/kg/d or 10 mg/kg/d twice daily for 5 days	Neuroprotection	Two doses of galantamine (1 mg/kg/day and 10 mg/kg/day) delayed the onset of neurologic impairments and decreased the mean neurological impairment scores ($p<0.05$). The dose-dependent benefit of galantamine was not significant.
Choi, et al. (2007) ²⁵	Minocycline: 45 mg/kg/d for 3 weeks	Neuroprotection	Minocycline reduced neuronal death and attenuated learning and memory impairment. % of eosinophilic cells vs. total cells in dentate gyrus was 52.38% (placebo-treated) vs. 12.70% (minocycline) ($p<0.05$).
Mievis, et al. (2007) ²⁷	Minocycline: 10 mg/kg/d for 14 days	Neuroprotection	No improvement in survival, weight loss, or motor function in treated mice. Minocycline failed to mitigate the ventricle enlargement and the striatal and cortical atrophies.

various cognitive deficit diseases. A study by Choi, et al. concluded that minocycline administration attenuated deficits in learning and memory in amyloid beta peptide(1-42)-infused rats.²⁵ Minocycline's neuroprotective proposed mechanism of action is related to its inhibitory activity on inflammation and/or apoptosis, both phenomena being closely associated with neurodegeneration.²⁶ A contradicting study by Mievis, et al. showed no benefit with minocycline in survival, weight loss, motor function, or mitigation of the ventricle enlargement, as well as the striatal and cortical atrophies induced by the transgene.²⁷ Omega-3 fatty acid EPA shows promising evidence of decreasing symptoms and motor dysfunction in 1 case report and 1 clinical trial.²⁸ Conversely, other trial data has found no significant difference in symptoms from the group of HD patients receiving 2g/day of ethyl EPA versus placebo.²⁹ Exploratory analysis revealed that a significantly higher number of patients in the per protocol cohort, treated with ethyl-EPA, showed stable or improved motor function though. Unsaturated fatty acids and minocycline are still being investigated for a possible role in future HD treatment strategies.

It has been proposed that CNS trauma during acute and chronic neurodegeneration can cause cytochrome *c* release from mitochondria into the cytoplasm of cells, activating an enzyme pathway ultimately leading to cell death. Multiple drugs have

been investigated which inhibit the release of cytochrome *c* from mitochondria, inhibit caspase activation, and block cell death. Wang and colleagues examined over 1040 compounds in an attempt to find drugs that inhibited cytochrome *c* release and lacked major side effects or penetration into the CNS.³⁰ The study identified 21 compounds, 16 of which were protective in a cellular model of cell death. A few of the more common drugs which showed inhibition of cytochrome *c* release and have some promise for the future were minocycline, doxycycline (Doryx[®]), methazolamide (Neptazane[®]), and melatonin. Ultimately, if cytochrome *c* release proves significant in HD, these pharmacological agents could emerge as alternative treatment options.

Another investigational medication in HD is trehalose, a supplement that inhibits cytokine release by working early in the inflammatory process and thus decreasing the limiting effects of HD on neurons. Trehalose is a disaccharide sugar found in nature that protects cells from a wide range of environmental stressors. It is postulated that trehalose increases the destruction of mHTT.³¹

Another experimental compound showing promise is a drug that inhibits HDAC 4 and thus is currently called HDACi 4b. HDAC 4 may be an important enzyme in promoting HD activity and HDACi 4b selectively binds HDAC 4 but does not inhibit the body's other important HDAC enzymes. Thomas, et

al. studied Huntington mice presenting with signs of motor dysfunction in which this compound was given to half of the mice while the other half were given placebo. A significant improvement in motor function scores was seen in the treated HD mice compared to placebo (288 vs. 250, respectively, $P=0.02$). All mice were trained on an AccuRotor rotarod at 3 months of age to establish baseline motor scores for each subject. These results were compared to the scores of the treatment and placebo groups once HDACi 4b was initiated. Hindlimb claspings, reduced global activity in a freely moving environment, hindlimb dystonia, and truncal dystonia (kyphosis) were all used as markers to establish motor scores. HDACi 4b caused a decrease in the expression of genes associated with cell death, cell cycle, and the immune response which could ultimately provide neuroprotection. HDACi 4b prevented dystonic posture and dramatically improved the physical appearance of the treatment group. Brain weight was significantly higher in the treatment group compared to placebo (407.3mg vs. 356.4mg, respectively, $P=0.045$). HDACi 4b has shown less toxicity and greater benefits in mice than other previous HDAC inhibitors.³²

SUMMARY

There is still much to be learned about HD and its treatment. Successful treatment for this disease is crucial since adult-onset HD usually runs its full terminal course in 10 to 30 years after signs and symptoms appear and in only 10 years with juvenile HD. Most patients become bedridden by the final stages of HD and normally die from complications such as pneumonia, heart failure, and injuries related to falls. HD is a serious disease that can present with symptoms of chorea, aggression, depression, cognitive deficits, along with many other physical and mental detriments. Tetrabenazine, typical and atypical antipsychotics, valproic acid, galantamine, memantine, amantadine, minocycline, doxycycline, HDACi 4b, and other drugs have shown promise in HD. The hope of investigational and future treatment options keeps the future bright for such a dark disease.

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DRUG UPDATES

Levetiracetam Going Generic

In January 2009, the FDA granted letters of approval for the production of generic levetiracetam subsequent to the patent expiration of Keppra® (UCB Pharma, Inc.; Brussels, Belgium). Generic levetiracetam is available as 250 mg, 500 mg, 750 mg, and 1,000 mg tablets as well as an oral solution of 100 mg/mL. The extended-release, oral formulation of levetiracetam, recently approved for adjunctive therapy in partial seizures among those aged > 16 years is not generically available at present and is marketed under the trade-name Keppra XR™.

Febuxostat (Uloric®) - Takeda Pharmaceuticals, Inc.

This month the FDA approved febuxostat for the chronic management of hyperuricemia in persons with gout. Febuxostat is an oral, selective xanthine oxidase inhibitor and differs from allopurinol in that it does not structurally resemble purines or pyrimidines. Look for more information on febuxostat and other emergent therapies for the management of hyperuricemia and gout in an upcoming edition of PharmaNote.

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