U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Parkinson Disease Agents. [Updated 2017 Jul 20].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Parkinson Disease Agents

Updated: July 20, 2017.

OVERVIEW

Parkinson disease is a progressive neurological condition characterized by slowness and paucity of movement (bradykinesia), muscle rigidity, resting tremors, and disordered posture. The onset is typically in the 6th or 7th decade of life with slow progression to akinesia, severe tremors, physical disability and death within 10 to 25 years of initial symptoms. Parkinson disease is common and affects approximately 1% of Americans above the age of 60 years. The cause of Parkinson disease is unknown, but is marked by loss of dopamine-containing neurons in the substantia nigra pars compacta of the brainstem and loss of normal dopaminergic neurotransmission. Therapy of Parkinson disease continues to evolve and has resulted in improved quality of life and survival.

The initial agents used for Parkinson disease were anticholinergic agents including trihexyphenidyl (Artane, Trihexy: 1949), benztropine (Cogentin: 1954), and biperiden (Akineton: 1959); their mechanism of action in Parkinsonism is not completely clear. With the increased understanding of the role of dopamine in the pathophysiology of Parkinsonism, agents that directly or indirectly affect dopaminergic transmission have been developed that have resulted in marked improvements in the management of symptoms of Parkinson disease. Levodopa (L-DOPA: 1970) is a metabolic precursor of dopamine and is the single most effective agent for Parkinson disease. It is usually combined with carbidopa (Sinemet: 1975), which increases the drug levels and half life of levodopa by inhibiting the amino acid decarboxylase that metabolizes levodopa peripherally. Dopaminergic receptor agonists are also beneficial in Parkinson disease and are often combined with levodopa/carbidopa. Dopamine receptor agonists currently available include bromocriptine (1978: Parlodel), pergolide (Permax: 1988), apomorphine (Apokyn: 2004) and more selective agonists for the D2 class of dopamine receptors – ropinirole (Requip: 1997), pramipexole (Mirapex: 1997) and rotigotine (Neupro which is formulated in a transdermal patch: 2007). More recently, inhibitors of catechol-O-methyltransferase (COMT) have been developed that block the major enzyme responsible for the metabolism of dopamine; these agents include tolcapone (Tasmar: 1998) and entacapone (Comtan: 2003). Dopamine is also metabolized by the monamine oxidases and selegiline (Atapryl: 2006) and rasagiline (Azilect: 2007) which are specific inhibitors of monamine oxidase (MAO) type B, and are used as an adjunctive therapy with levodopa in therapy of Parkinson disease. Amantadine (Symmetrel: 1987) also has activity in Parkinson disease, perhaps through stimulation of release of dopamine in the substantial nigra. It is discussed separately as an anti-influenza agent. Other agents used in the management of Parkinson disease are used to treat specific complications such as psychosis (pimavanserin: Nuplazid, 2016) and postural hypotension (droxidopa: Vectibix, 2014).

Most of the drugs used to treat Parkinson disease have little potential for hepatotoxicity and are rare causes of clinically apparent acute liver injury, the exception being tolcapone. The full references on hepatotoxicity and safety of the drugs for Parkinson disease are given in the discussion of the individual agents listed below.

- Anticholinergic Agents: Benztropine, Biperiden, Trihexyphenidyl
- Dopamine Precursors: Levodopa and Carbidopa
- Dopamine Receptor Agonists: Apomorphine, Bromocriptine, Pergolide, Pramipexole, Ropinirole, Rotigotine
- Selective MAO inhibitors: Rasagiline, Safinamide, Selegiline
- COMT inhibitors: Entacapone, Tolcapone
- Others: Amantadine, Diphenhydramine, Droxidopa, Pimavanserin, Rivastigmine

ANNOTATED BIBLIOGRAPHY

References updated: 20 July 2017

Zimmerman HJ. Antiparkinsonism drugs. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 715-7.

(Expert review of hepatotoxicity published in 1999; among anticholinergic agents, "only trihexyphenidyl has been incriminated in hepatic injury"; other antiparkinsonism drugs discussed include levodopa, lergotrile [no longer available], pergolide and bromocriptine).

Larrey D, Ripault MP. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier Inc, 2013, pp. 443-62.

(Review of hepatotoxicity of agents acting on the central nervous system).

Standaert DG, Roberson ED. Treatment of central nervous system degenerative disorders. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 609-28.

(Textbook of pharmacology and therapeutics).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none were attributed to agents used for Parkinson disease).

In brief: transdermal rotigotine (Neupro). Med Lett Drugs Ther 2012; 54 (1397): 68. PubMed PMID: 22907181.

(Concise report mentions that transdermal rotigotine patches were withdrawn in 2008 because of crystallization of the drug on the patch and an improved formulation was introduced in 2012).

Drugs for Parkinson's disease. Treat Guidel Med Lett 2013; 11 (135): 101-6. PubMed PMID: 24165688.

(Concise review of recommendations for therapy of Parkinson disease with description of mechanisms of action, efficacy and adverse events).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America: an analysis of published reports. Ann Hepatol 2014; 13: 231-9. PubMed PMID: 24552865.

(Among 176 reports of drug induced liver injury from Latin America published between 1996 and 2012, none were attributed to an agent to treat Parkinson disease).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury from the US enrolled in a prospective database between 2004 and 2012, none were attributed to an agent used to treat Parkinson disease).