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Pharmacokinetic Drug Interactions of Valbenazine and its Active Metabolite

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Cytochrome P450

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Cytochrome P450

- Cytochrome P450 (CYPs) are a superfamily of enzymes that play a key role in metabolism of medications[1,2]

- CYPs are the most common drug-metabolizing enzymes involved in:[2,3]
  - Transforming substances to inactive metabolites before further elimination
  - Synthesizing pharmacologically inactive prodrugs into active forms
  - Biosynthesis of endogenous compounds (e.g., bile acid and cholesterols)

- CYP enzymes are mainly expressed in the liver and intestine, the two main sites of overall metabolism and elimination of medications[3]

1. McDonnell AM, et al. J Adv Pract Oncol. 2013;4(4):263-268. 2. Manikandan P, et al. Curr Drug Targets. 2018;19(1):38-54. 3. Song Y, et al. Clin Pharmacokinet. 2021 May;60(5):585-601.

CYP Inducers and Inhibitors

- Medications that share a common metabolic pathway have the potential for drug-drug interactions[1]

- Medications with CYP activity may act as substrates, inducers and/or inhibitors for a specific CYP enzymatic pathway[1,2]
  - CYP enzyme inhibition is more common than induction
  - CYP induction and inhibition are classified as strong, moderate, or weak depending on the magnitude of impact on the substrate[3]

Substrates[3,4]	Inducers[1,2]	Inhibitors[1,5]
Molecules/medications that are metabolized by CYPs. Exposure may be changed by an inducer/inhibitor	Medications that **induce** CYPs may **accelerate metabolism**, potentially **reducing** exposure and weakening efficacy	Medications that **inhibit** CYPs may **decrease metabolism,** potentially **increasing** exposure and risk of drug toxicity

1. McDonnell AM, et al. J Adv Pract Oncol. 2013;4(4):263-268. 2. Song Y, et al. Clin Pharmacokinet. 2021 May;60(5):585-601. 3. United States Food and Drug Administration. Guidance for Industry. Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions. January 2020. Clinical Pharmacology. Accessed on January 10, 2022. 4.Manikandan P, et al. Curr Drug Targets. 2018;19(1):38-54. 5. Almazroo OA, et al. Clin Liver Dis. 2017 Feb;21(1):1-20.

Strong CYP Inhibitors/Inducers May Cause Drug-Drug Interactions

CYP2D6[1-4]	
Strong Inhibitors	
Medication	**Class**
Bupropion	Atypical antidepressants
Fluoxetine	SSRIs
Paroxetine	
Duloxetine	SNRIs
Terbinafine	Antifungal
Quinidine	Antiarrhythmic
Haloperidol	Antipsychotics
Methadone	Opioids
Tetrahydrocannabinol (THC)	Cannabinoids
Cannabidiol (CBD)	

CYP3A4[1,2,4,5]			
Strong Inducers		**Strong Inhibitors**	
Medication	**Class**	**Medication**	**Class**
Carbamazepine	Anticonvulsants	**Itraconazole**	Antifungals
Oxcarbazepine		**Ketoconazole**	
Phenytoin		**Posaconazole**	
Apalutamide	Androgen receptor inhibitors	**Voriconazole**	
Enzalutamide		**Telithromycin**	Antibiotics
Lumacaftor		**Clarithromycin**	
Ivosidenib	Antineoplastics	**Troleandomycin**	
Mitotane		**Ceritinib**	Antineoplastics
Phenobarbital	Barbiturates	**Idelalisib**	
Pentobarbital		**Nefazodone**	Atypical antidepressant
Rifampicin	Antibiotics	**Ritonavir**	Antiviral
St. John's Wort	Herbal	**Cobicistat**	
		Nelfinavir	
		Cannabidiol	Cannabinoid

CYP, cytochrome P450; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor
*These tables are prepared to provide examples of inhibitors and inducers and is not intended to be an exhaustive list

1. Hoeft D. *Mental Health Clinician*. 2014;4(3):118-130. 2. United States FDA. Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers. Accessed January 26, 2022. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2 3. Ingelman-Sundberg, M. *Pharmacogenomics*. 2005;5(1):6-13. 4. Nasrin S, et al. *Drug Met and Disp.* 2021;49(12):1070-1080. 5. Ganjoo, KN, et al. *Biologics*. 2007;1(4):335-346.

Valbenazine Metabolism and Drug Interactions

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Valbenazine: Drug Interactions

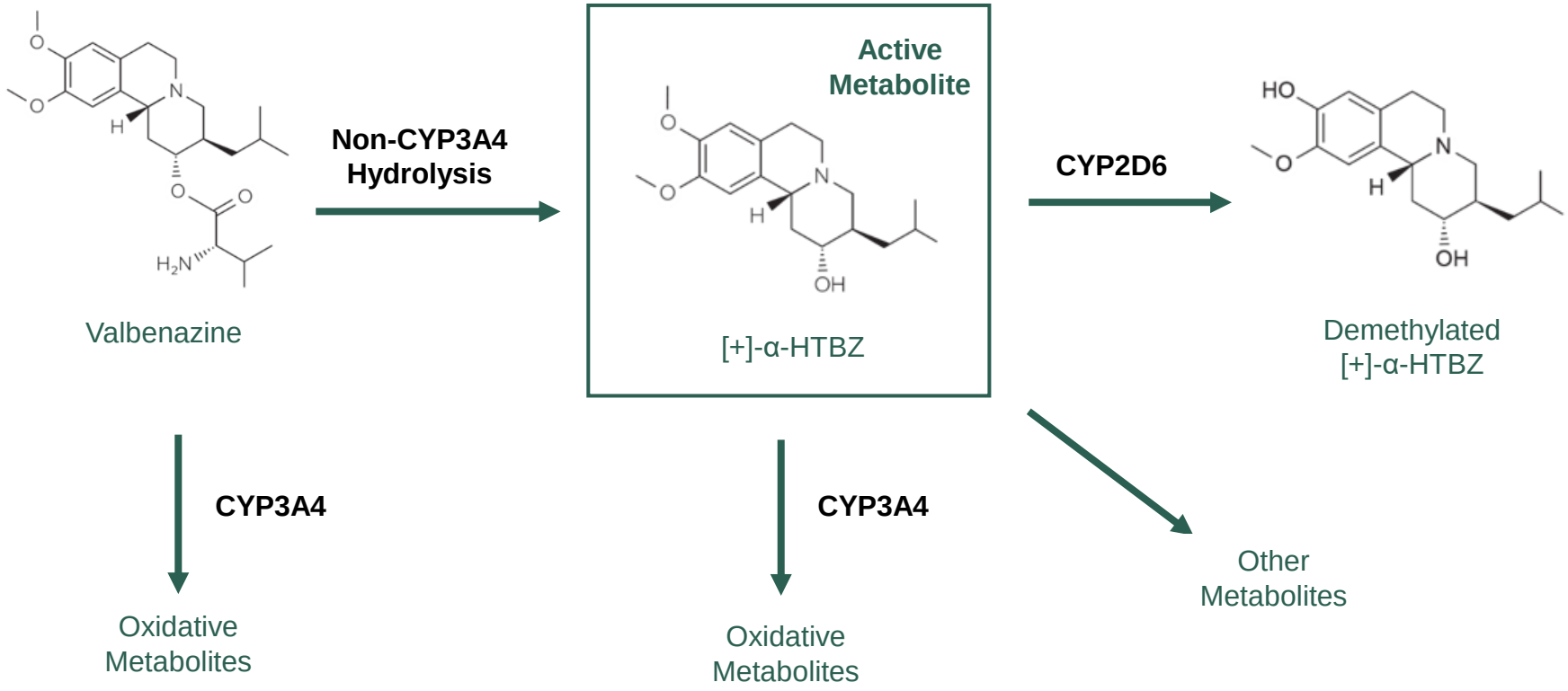
Drugs Having Clinically Important Interactions With Valbenazine	
Strong CYP3A4 Inhibitors	
Clinical impact	Concomitant use of valbenazine with strong CYP3A4 inhibitors increased the exposure (C_{max} and AUC) to valbenazine and its active metabolite compared with the use of valbenazine alone. Increased exposure of valbenazine and its active metabolite may increase the risk of exposure-related adverse reactions.
Prevention or management	Reduce valbenazine dose when valbenazine is coadministered with a strong CYP3A4 inhibitor.
Strong CYP2D6 Inhibitors	
Clinical impact	Concomitant use of valbenazine with strong CYP2D6 inhibitors increased the exposure (C_{max} and AUC) to valbenazine's active metabolite compared with the use of valbenazine alone. Increased exposure of active metabolite may increase the risk of exposure-related adverse reactions.
Prevention or management	Reduce valbenazine dose when valbenazine is coadministered with a strong CYP2D6 inhibitor.
Strong CYP3A4 Inducers	
Clinical impact	Concomitant use of valbenazine with a strong CYP3A4 inducer decreased the exposure of valbenazine and its active metabolite compared to the use of valbenazine alone. Reduced exposure of valbenazine and its active metabolite may reduce efficacy.
Prevention or management	Concomitant use of strong CYP3A4 inducers with valbenazine is not recommended.

AUC, area under the curve; C_{max}, maximum observed concentration; CYP, cytochrome P450.

INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., San Diego, CA.

Valbenazine Metabolism

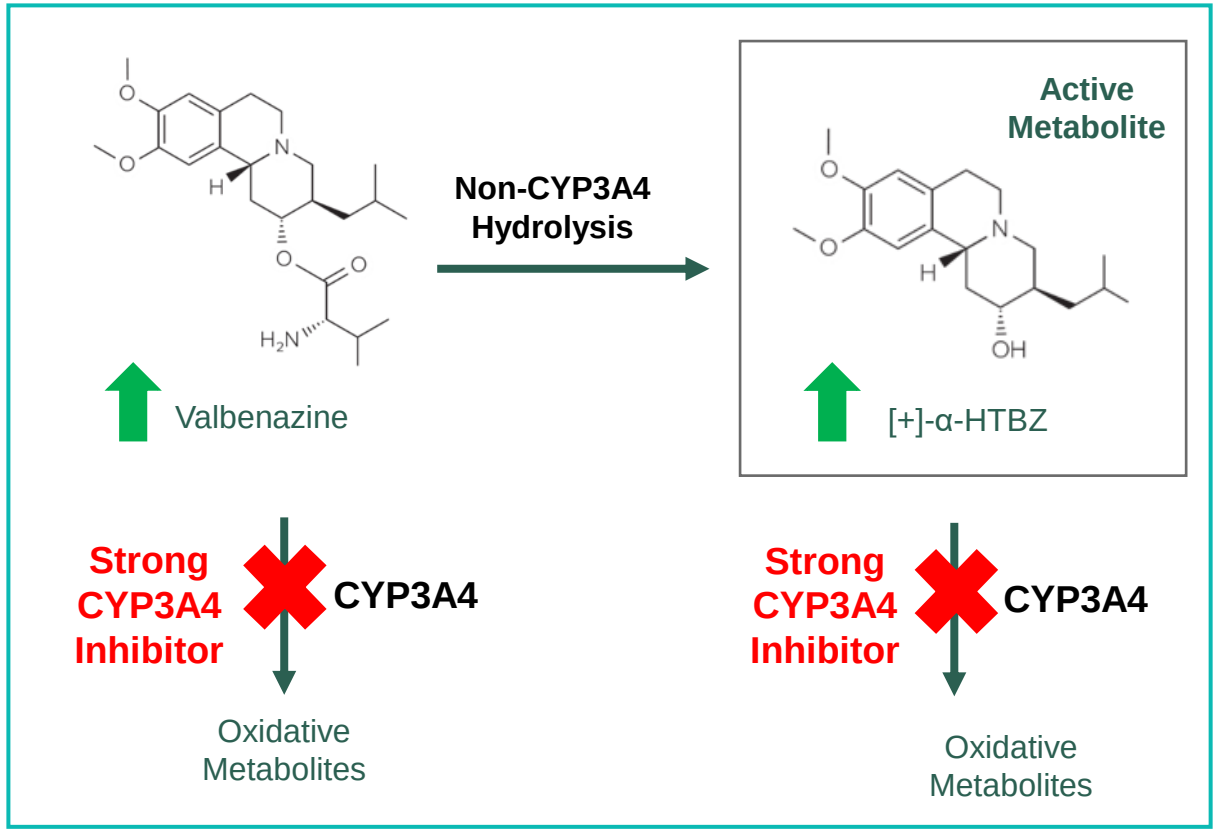
- Valbenazine is converted to a single active metabolite [+]-α-dihydrotetrabenazine ([+]-α-HTBZ) through the loss of L-valine by hydrolysis
  - [+]-α-HTBZ is metabolized in part by cytochrome P450 (CYP) 2D6



Loewen G, et al. ASCP 2017; Miami, FL.

Valbenazine Metabolism[1]: Strong 3A4 Inhibitor Interaction

- Strong CYP3A4 inhibitors can increase the exposure of valbenazine and its active metabolite[2]



In patients receiving a strong CYP3A4 inhibitor, the recommended valbenazine dosage is 40 mg daily[2]

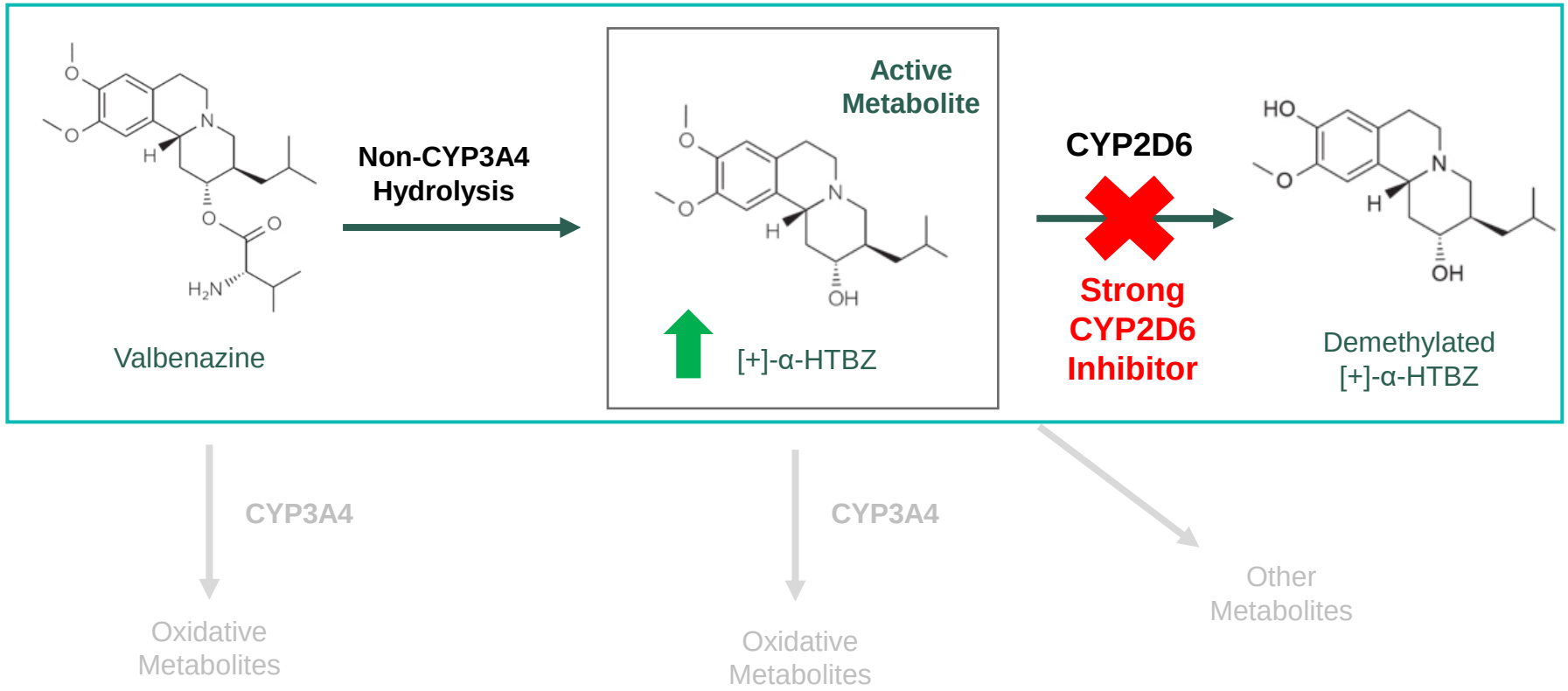
Strong CYP inducers and inhibitors can affect the exposure of valbenazine, whereas valbenazine has minimal potential to impact the metabolism of concomitant CYP medications[1]

CYP, cytochrome P450.

1. Loewen G, et al. ASCP 2017; Miami, FL. 2. INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., San Diego, CA.

Valbenazine Metabolism[1]: Strong 2D6 Inhibitor Interaction

- Strong CYP2D6 inhibitors can increase the exposure of valbenazine and its active metabolite[2]



In patients receiving a strong CYP2D6 inhibitor, the recommended valbenazine dosage is 40 mg daily[2]

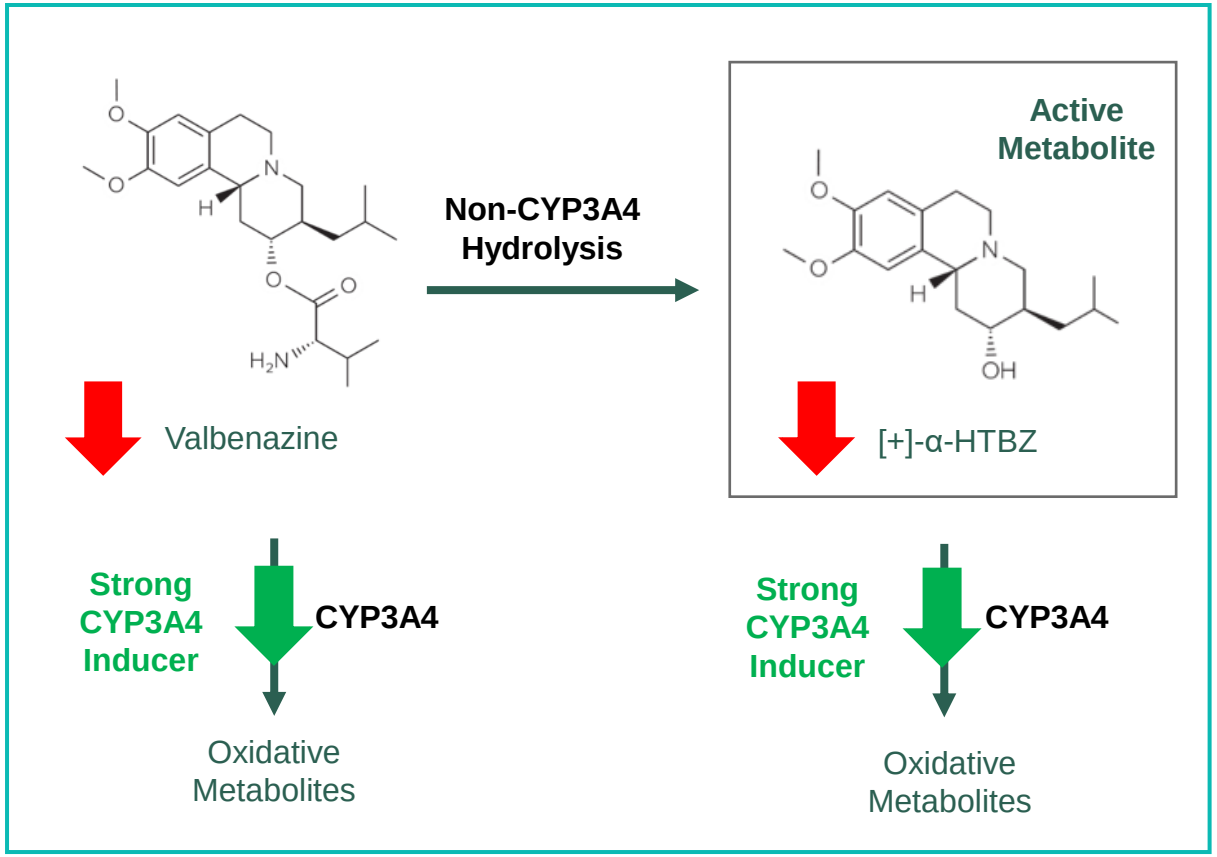
Strong CYP inducers and inhibitors can affect the exposure of valbenazine, whereas valbenazine has minimal potential to impact the metabolism of concomitant CYP medications[1]

CYP, cytochrome P450.

1. Loewen G, et al. ASCP 2017; Miami, FL. 2. INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., San Diego, CA.

Valbenazine Metabolism[1]: Strong 3A4 Inducer Interaction

- Strong CYP3A4 inducers can decrease exposure of valbenazine and its active metabolite[2]



In patients receiving a strong CYP3A4 inducer, valbenazine is not recommended[2]

Strong CYP inducers and inhibitors can affect the exposure of valbenazine, whereas valbenazine has minimal potential to impact the metabolism of concomitant CYP medications[1]

CYP, cytochrome P450.

1. Loewen G, et al. ASCP 2017; Miami, FL. 2. INGREZZA® (valbenazine). Package insert. Neurocrine Biosciences, Inc., San Diego, CA

Other Drug Interactions

Drugs Having Clinically Important Interactions With Valbenazine	
Digoxin	
Clinical impact	Concomitant use of valbenazine with digoxin increased digoxin levels because of inhibition of intestinal P-glycoprotein (P-gp).
Prevention or management	Digoxin concentrations should be monitored when coadministering valbenazine with digoxin. Increased digoxin exposure may increase the risk of exposure-related adverse reactions. Dosage adjustment of digoxin may be necessary.
Monoamine Oxidase Inhibitors (MAOIs)	
Clinical impact	Concomitant use of valbenazine with MAOIs may increase the concentration of monoamine neurotransmitters in synapses, potentially leading to increased risk of adverse reactions, such as serotonin syndrome, or attenuated treatment effect of valbenazine.
Prevention or management	Avoid concomitant use of valbenazine with MAOIs, or within 14 days of discontinuing therapy with an MAOI.

MAOI, monoamine oxidase inhibitor

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