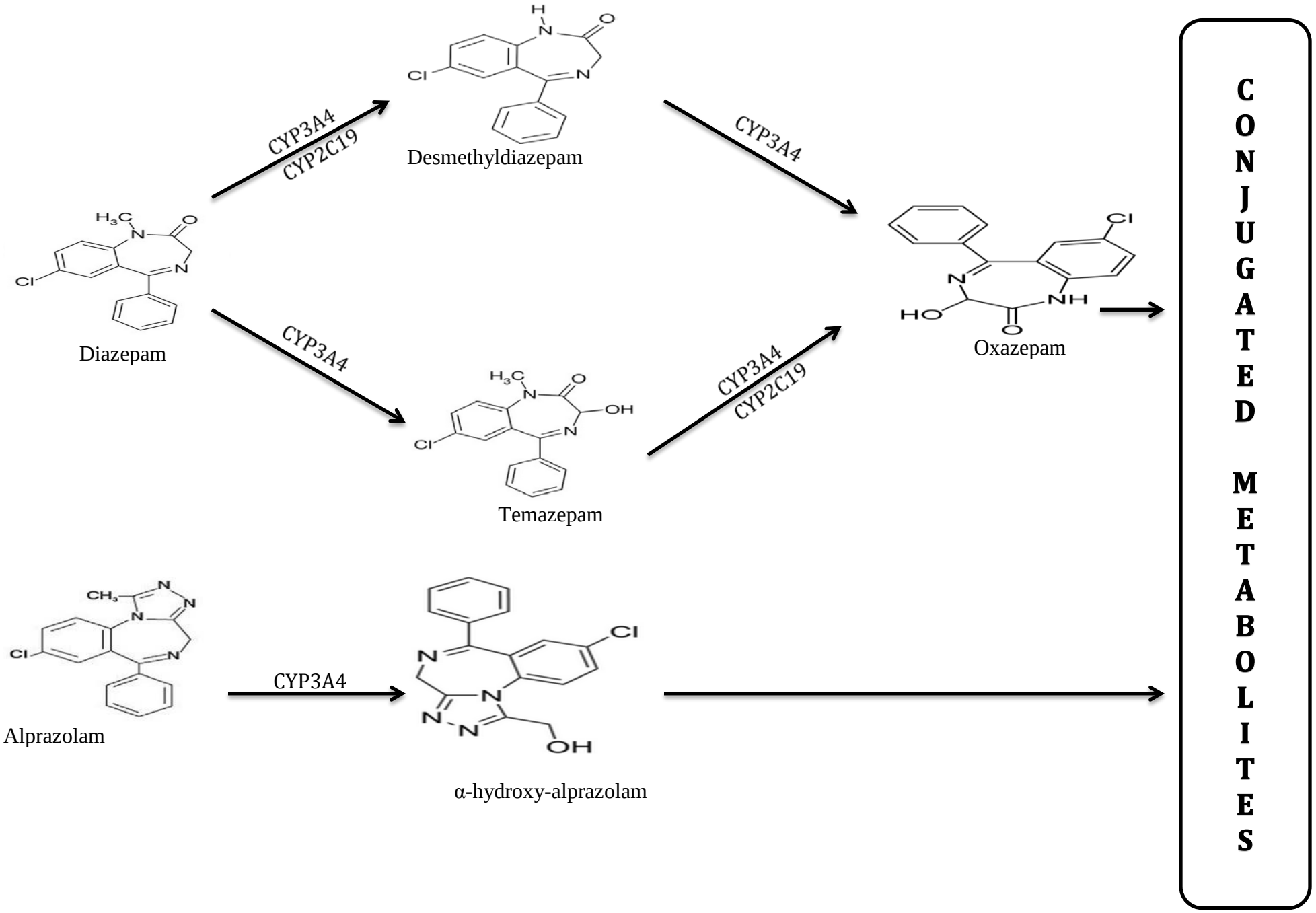
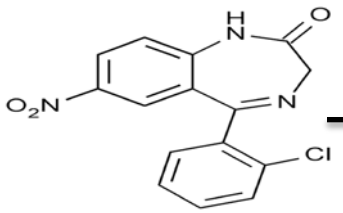
Benzodiazepine Metabolism and Pharmacokinetics

Complied by Mena Raouf, Pharm.D. Candidate, 2016, reviewed and edited by Dr. Jeffrey Fudin

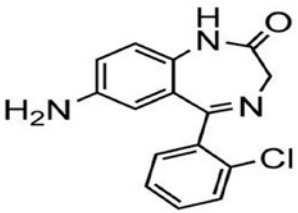
Benzodiazepines that undergo Phase I metabolism





Clonazepam

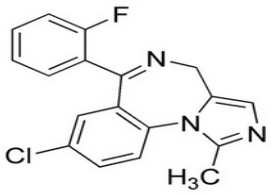
CYP3A4



7-aminoclonazepam

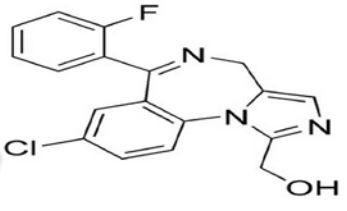
NAT2

7-acetamido clonazepam

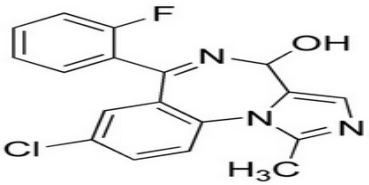


Midazolam

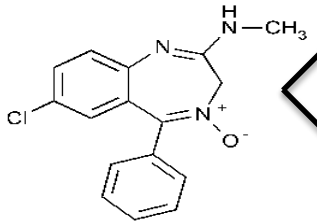
CYP3A4



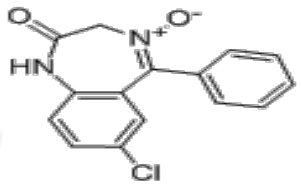
1- hydroxy-midazolam



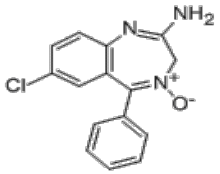
4- hydroxy-midazolam



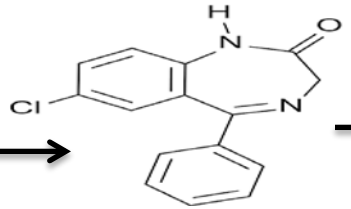
Chlordiazepoxide
(pro-drug)



Demoxepam

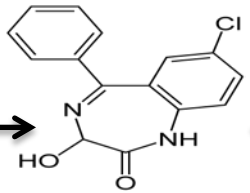


Nor-chlordiazepoxide



Des-methyl-diazepam

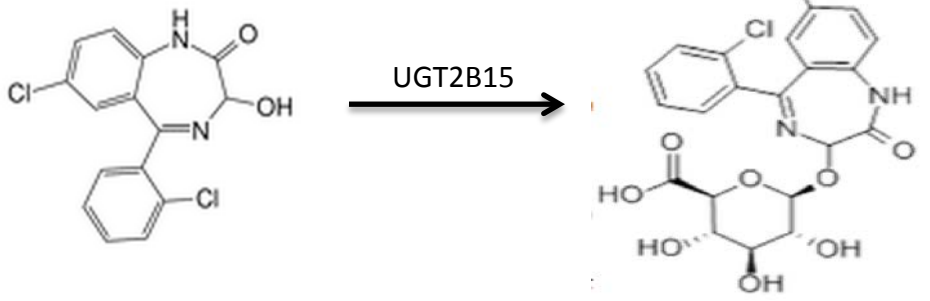
CYP 3A4



Oxazepam

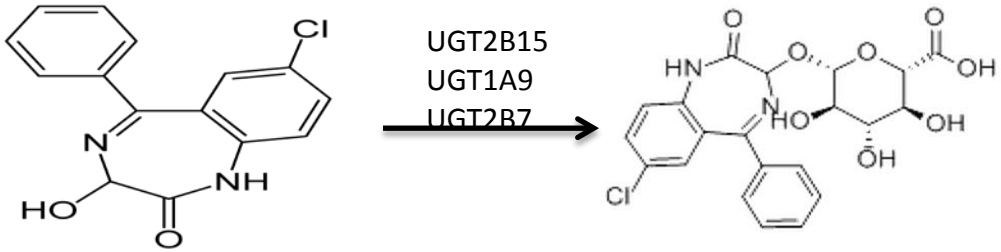
CONJUGATED METABOLITES

Benzodiazepines that undergo Phase II metabolism (LOT)



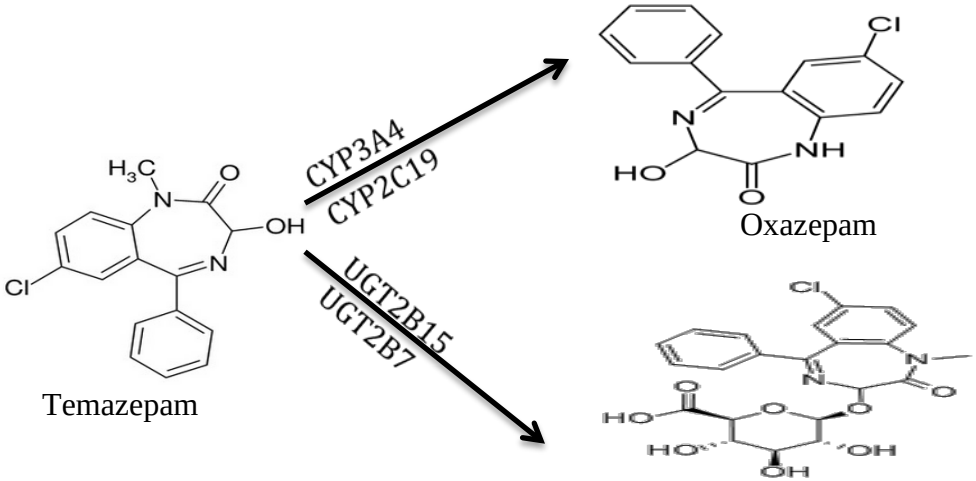
Lorazepam

Lorazepam-glucuronide



Oxazepam

Oxazepam-glucuronide



Temazepam

Oxazepam

Temazepam-glucuronide

Table 1: Metabolism and Elimination of select benzodiazepines

Parent Drug	Approximate Equivalent Dose	Time to Peak Plasma Level following oral administration (Hours)	Metabolic pathway	Enzymes	Elimination half-life of Parent Drug (Hours)	Metabolites	Detection window in Urine Drug Screening (Days)
Benzodiazepine Anxiolytics							
Diazepam	5mg	0.5-2	Demethylation Hydroxylation	CYP 2C19 CYP 3A4	20-80	Desmethyldiazepam (major) Temazepam (minor) Oxazepam (minor)	10-30 days [6,8]
Alprazolam	0.5mg	1-2	Hydroxylation	CYP 3A4	12-15 hours	α-hydroxy-alprazolam	5 days
Clonazepam	0.25mg	1-4	Nitroreduction Acetylation	CYP 3A4 NAT2	30-40	7-amino-clonazepam	5 days
Oxazepam	15mg	2-4	Conjugation	UGT2B15 UGT1A9 UGT2B7	5-20	Oxazepam-glucuronide	5 days
Temazepam	15mg	1-2	Conjugation	UGT2B7 UGT2B15 2C19 3A4	3-13	Oxazepam	1-4 days
Lorazepam	1mg	2-4	Conjugation	UGT2B15	10-20	Lorazepam glucuronide	5 days
Chlordiazepoxide	25mg	1-4	N-demethylation Hydroxylation	CYP3A4	6.6-28	Desmethylchlordiazepoxide demoxepam Desmethyldiazepam (active) Oxazepam (active)	5-30 days[6,8]

Midazolam	5mg		Hydroxylation	CYP 3A4	1-4	4- Hydroxy-midazolam 1- Hydroxy-midazolam	0.5-2 days
Benzodiazepine Sedative Hypnotics							
Triazolam	0.25mg	15-30 minutes	Hydroxylation	CYP3A4	1.5-5.5	4-hydroxytriazolam α hydroxytriazolam	7-15 hours.
Flurazepam	15mg	30-60 minutes	oxidation	CYP3A4	2.3 hours	Ndesalkylflurazepam Flurazepam-aldehyde	4-16 days
Estazolam	1-2mg	1.5-2 hours	Oxidation	CYP3A4	10-24 hours	1-oxo-estazolam 4-hydroxy-estazolam	1-4 days
Quazepam	10mg	1-2 hours	Oxidation	CYP3A4, CYP2C9, and CYP2C19	39-73 hours	N-desalkyl-2-oxoquazepam 2-oxoquazepam	2-4 days
Non Benzodiazepine Sedative Hypnotics "Z-Drugs"							
Zolpidem	5-10mg	30 minutes	Oxidation	CYP 3A4 , CYP2C9, CYP2D6, CYP2C19	2.5 hours	Zolpidem carboxylic acid	1-3 days
Zaleplon	5-10mg	15-30 minutes	Oxidation	Aldehyde Oxidase (major) CYP3A4	1 hour	5-oxo-zaleplon Desethylzaleplon 5-oxo-desethylzaleplon	
Eszopiclone	1mg	15-45 minutes	Oxidation Demethylation	CYP 3A4 (major) CYP2E1	6-7 hours	(S)-desmethylzopiclone *(S)*-zopiclone-N-oxide	

Table 2: Benzodiazepine drug-drug interactions

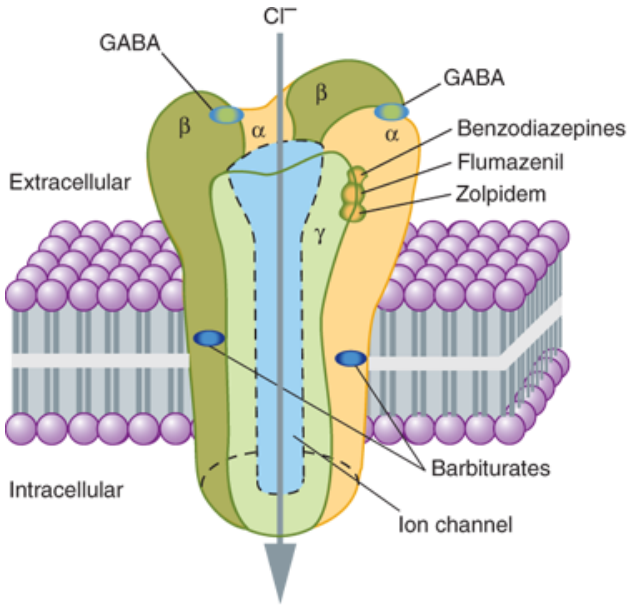
CYP family	Substrates	Inhibitors	Inducers
CYP3A4	Alprazolam Midzolam Temazepam Triazolam Zaleplon Zolpidem	Azole antifungals Macrolides Amiodarone Diltiazem Verapamil Protease Inhibitor	Carbamazepine Phenobarbital Phenytoin Rifampin
CYP 2C19	Diazepam	Omeprazole Oxcarbazepine Topiramate	Dexamethasone Phenobarbital Phenytoin Rifampin
UGT	Lorazepam Oxazepam		Lamotrigine Phenobarbital Phenytoin Rifampin

Benzodiazepines

Benzodiazepines are one of the most commonly prescribed medications to treat anxiety, insomnia, and other conditions in the United States. [1,2] In 2008, approximately 5.2% of US adults (18-80 years old) have used benzodiazepines, and the percentage increases with age.[1] Benzodiazepine core chemical structure is composed of diazepine fused to a benzene ring. Different benzodiazepines have different side chains, which determine their pharmacokinetic profile. Benzodiazepines are used for their anxiolytic, antiepileptic, muscle relaxant, and hypnotic effects. Apart from their medical benefit, they have the potential for abuse and misuse. Benzodiazepines with fast onset and short half-life (alprazolam, triazolam) cause a "rush" due to rapid increase in plasma concentration and increased craving due to short duration of effect, thereby increasing abuse potential. Benzodiazepines with high lipophilicity (eg: diazepam) can penetrate CNS tend to have high abuse potential as well.[2,3,6]

Benzodiazepines bind to the to γ-aminobutyric acid type A receptor (GABA-A) at the alpha-subunit and potentiate GABA activity, thereby increasing conductance of the chloride channel and inhibiting neuronal excitability, which corresponds to their anxiolytic and muscle-relaxing effects GABA-A receptors throughout the CNS consist of various combinations of α,β, γsubunits. The most common isoform of GABA-A receptor consists of two α1 subunits, two β2 subunits, and one γ2 subunit. Benzodiazepines bind to α2, α3, and α5 subunits of the GABA-A receptor. Benzodiazepines are allosteric modulators that require GABA to be bound to its receptor. Non-benzodiazepine sedative hypnotics "Z-drugs" including zolpidem, eszopiclone, and zaleplon are selective for α_1 subunit. However, eszopiclone has been also found to bind to other GABA-A receptor subunits similar to benzodiazepines. [2,3]

Figure 1: GABA receptor



Source: Bertram G. Katzung, Anthony J. Trevor: Basic & Clinical Pharmacology, 13th Ed.
www.accesspharmacy.com

Table 3: GABA-A receptor subtypes[30,31]

Alpha subunit	% of CNS GABA-A receptors	Function
α_1	60	Sedation, amnesia, partial anticonvulsant activity
α_2	15-20	Anxiolytic, muscle relaxant
α_3	10-15	Myorelaxation (only at high doses)
α_4	<5	Insensitive to benzodiazepines
α_5	<5	Partial myorelaxation
α_6	<5	Insensitive to benzodiazepines

Benzodiazepine Metabolism

Benzodiazepines undergo Phase I and Phase II metabolic pathways: hepatic oxidation and reduction (by cytochrome P450) and glucuronide conjugation. Alprazolam, triazolam, midazolam, and diazepam undergo hydroxylation while clonazepam undergoes nitroreduction. CYP2C19 and CYP3A4 are the major players in the metabolism of benzodiazepines that undergo phase I metabolism (figure 1). Phase I metabolism tends to be reduced in the elderly, along with polypharmacy, predisposing elderly patients to CYP450 related interactions. However, phase II metabolism remains relatively preserved in the elderly.. Benzodiazepines that undergo phase II glucuronidation include lorazepam oxazepam temazepam (LOT) and are the recommended benzodiazepines in the elderly. [2,3]

Adverse effects

This is not exhaustive list but it includes common side effects

- Drowsiness
- Ataxia
- Memory impairment: anterograde amnesia most commonly reported with alprazolam[14] and diazepam[19]
- Nausea
- Fatigue
- Cognitive impairment: most commonly reported with alprazolam[14]
- Decreased libido
- Hallucination
- Sleep related activities: ex: sleep driving, sleep eating, sleep sex are more commonly associated with the Z-drugs.

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