“We are healed of a suffering only by expressing it to the full.”

Marcel Proust, novelist (1871-1922)
Appendix:
Medications Seldom Used in Children & Adolescents

Medications Covered
- Benzodiazepines
- Buspirone
- Gabapentin
- Modafinil
- Monoamine oxidase inhibitors
- Topiramate
- Tricyclic antidepressants

Learning Objectives
- For each medication covered:
  1. Summarize the evidence regarding the medication's efficacy in children and adolescents
  2. Identify adverse effects, risks, and necessary precautions associated with the medication
  3. Explain how to initiate, titrate, and monitor the medication

Outline
- For each medication covered:
  - Indications & clinical use
  - Pharmacodynamics & pharmacokinetics
  - Efficacy
  - Adverse effects
  - Contraindications & drug interactions
  - Monitoring
  - Dosing

Benzodiazepines

Health Canada: General Indications

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*Refer to individual product monographs for more detailed information.

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Health Canada: Pediatric Indications

- CPS:
  - “Some benzodiazepines are used in children for many of the same indications as for adults. They share the same precautions as for adults, but can also cause paradoxical excitation in children. Specialized references should be consulted for detailed information.”
  - Lorazepam and nitrazepam are not recommended for use in individuals under 18 years of age
  - For clobazam, clonazepam, clorazepate, and diazepam, recommendations regarding use in pediatric populations are not provided

Clinical Use in Child Psychiatry

- BZ are used much more frequently in adults than in children and adolescents
- BZ have been used in youth as:
  - A treatment for anxiety disorders, sleep-related disorders, aggression, and catatonia
  - An adjunctive treatment for mania, psychosis, and OCD
  - However, data supporting these uses are minimal
- No specific clinical guidelines exist for treating any of the childhood psychiatric disorders with BZ

Pharmacodynamics

- Benzodiazepines (BZ) act throughout the CNS
- Proposed relationships between sites of action and effects:
  - Limbic and cortical regions: anxiolytic effects
  - Brainstem or reticular formation: sedative effects
  - Striatum, globus pallidus, and substantia nigra: anticonvulsant effects
  - Hippocampus: memory effects
  - Cerebellum: ataxia
  - Spinal cord: muscle relaxation

Pharmacodynamics (cont.)

- All BZ have similar pharmacodynamic properties and act mainly on γ-aminobuteric acid A (GABA_A) receptors
- GABA_A receptors mediate fast synaptic inhibition via transmitter-gated chloride ion channels
- The primary mechanism by which BZ have their effect on GABA_A receptors is “positive allosteric modulation”

Pharmacodynamics (cont.)

- Explanation of “positive allosteric modulation”:
  - BZ and GABA bind to separate sites on the GABA_A receptor complex
  - When a BZ occupies the BZ site on the GABA_A receptor complex, GABA’s ability to open the chloride channel ↑
  - With greater opening of the chloride channel, cellular excitability ↓
- Because of the extensive inhibitory role of GABA in the CNS, BZ may also alter the turnover of neurotransmitters such as NE and 5-HT

Pharmacokinetics

- BZ are highly lipid-soluble, which allows them to cross the BBB quickly
- Consequently, with oral dosing, the rate-limiting step in the onset of action is absorption:
  - Most BZ are completely absorbed from the GI tract (the one exception is clorazepate), but the rate of absorption, and thus the onset of action, varies
  - Diazepam is absorbed the fastest (15-30 minutes in children)
  - Most BZ (exceptions are lorazepam and midazolam) are not consistently absorbed from IM injection
  - When BZ are given IV, the onset of action is almost immediate

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Pharmacokinetics (cont.)

• BZ are highly bound to plasma proteins

• Because BZ are redistributed until over 95% of the drug is outside the blood circulation and the brain, it is the distribution $T_{1/2}$ that is most important in determining the duration of action of each BZ

• However, it is the elimination $T_{1/2}$ that is most studied and best known

Pharmacokinetics (cont.)

• Almost all BZ are metabolized primarily by the liver and undergo phase I (mainly oxidation) and/or phase II (glucuronidation) reactions

• For example, diazepam, chlordiazepoxide, and flurazepam undergo both phase I and phase II reactions

• In contrast, lorazepam, oxazepam, and temazepam (mnemonic: “LOT”) are metabolized by phase II reactions alone and are therefore better tolerated by patients with liver impairment

• Recall (Intro Seminar) that phase II reactions may occur in almost any organ, and because they do not depend solely on hepatic function, their efficiency does not vary with age

Efficacy: Anxiety Disorders

• Small open trials suggested that various BZ (chlordiazepoxide, alprazolam, clonazepam) may be beneficial in children and adolescents with a variety of anxiety disorders or symptoms:
  – Kraft et al., 1965
  – Pfefferbaum et al., 1987
  – Simeon et al., 1987
  – Biederman et al., 1987
  – Kutcher & MacKenzie, 1988
  – Klein & Last, 1989
  – Bernstein et al., 1990
  – D’Amato, 2001

Efficacy: Anxiety Disorders (cont.)

• However, all 3 DBPC studies were negative:
  – Bernstein et al., 1990 (alprazolam vs. imipramine vs. PBO for school refusal)
  – Simeon et al., 1992 (alprazolam vs. PBO for separation anxiety, overanxious, or avoidant disorder)
  – Graae et al., 1994 (clonazepam vs. PBO crossover trial for a variety of anxiety disorders)

• Limitations of these studies:
  – Small sample sizes
  – Heterogeneous samples, i.e., children with different anxiety disorders included
  – High PBO response rates
Efficacy: Sedation/Anxiolysis Before Procedures

• Finley et al., 2006:
  – RCT of midazolam (midazolam+acetaminophen vs. acetaminophen alone) in 40 children (4-6 years old) scheduled for myringotomy
  – Children who received midazolam reacted significantly less to induction of anesthesia
• Roelofse et al., 1990:
  – DBPC trial of rectal midazolam (0.25 vs. 0.35 vs. 0.45 mg/kg) in 80 children (2-10 years old) undergoing dental extraction
  – With all doses of midazolam, good anxiolysis, sedation, and cooperation were obtained in most patients

Efficacy: Night Terrors

• Popoviciu & Corfariu, 1983:
  – PBO-controlled trial of midazolam 15 mg in 15 children (6-15 years old) with night terrors
  – Midazolam resulted in:
    • ↑ total sleep time
    • Favourable modification in sleep architecture
    • ↓ number of nocturnal arousals
    • Night terrors eliminated in all but one subject
    • No side effects

Adverse Effects

• Sedation (most common)
• Lightheadedness, vertigo
• Nausea, vomiting, epigastric distress
• Transient hypotension
• Blurred vision
• Sexual dysfunction
• Vivid dreams, changes in sleep architecture (although these do not appear to ↓ restfulness)
• Cognitive impairment: ↓ attention, ↓ encoding of new information, and anterograde amnesia (rare)

Adverse Effects (cont.)

• ↓ motor coordination, ataxia, ↑ reaction time
• Disinhibition (see next several slides)
• Delirium
• Psychosis (rare)
• Withdrawal when discontinued abruptly (can be dangerous)
• Respiratory depression and death when combined with other drugs such as alcohol (Finkle et al., 1979; Hobbs et al., 1996)
  – Note: Even at high doses, BZ taken alone do not appear to cause respiratory depression (Barnett & Riddle, 2003)

Risk of Disinhibition: How Worried Should You Be?

• The general risk of disinhibition with BZ is estimated to be <1% (Mancuso et al., 2004)
• Clinical experience suggests that the risk may be greater in children compared to adults, but this has not been well studied
• Some clinical experience suggests that, as with alcohol, disinhibition associated with BZ can be overcome by increasing the dose (Barnett & Riddle, 2003)
• On the other hand, some data (Roelofse et al., 1990) suggest that higher doses of a BZ are associated with ↑ risk of disinhibition in children

BZ and Disinhibition (cont.)

• Petti et al., 1982:
  – PBO-controlled crossover trial of chlordiazepoxide in 9 “severely disturbed” inpatient boys (7-11 years old) with various diagnoses
  – Evidence of disinhibition with chlordiazepoxide:
    • 5 developed hyperactivity
    • 4 developed extreme mood lability
    • 3 developed ↑ aggression
BZ and Disinhibition (cont.)

• BZ for anxiety:
  – Bernstein et al., 1990:
    • With alprazolam, no subject had adverse effects rated higher than “mild, does not interfere with functioning”
  – Simeon et al., 1992:
    • With alprazolam, adverse effects were described as “few, mild, and transient”
  – Graae et al., 1994:
    • With clonazepam, 10 of 15 subjects developed irritability, oppositional behaviour, or severe disinhibition (including 1 with attempted self-injury)

BZ and Disinhibition (cont.)

• BZ for sedation/anxiolysis before procedures:
  – Roelofse et al., 1990:
    • Disinhibition reactions were observed in about one-quarter taking midazolam, particularly those in the high-dose (0.45 mg/kg) group
  – Massanari et al., 1997:
    • 2617 children (1-17 years old) received midazolam and meperidine before endoscopy; 36 (1.4%) experienced paradoxical reactions
  – Saltik et al., 2000:
    • 222 children (2.5-18 years old) received midazolam and meperidine before endoscopy; 25 (11%) experienced paradoxical reactions

Contraindications

• Hypersensitivity to BZ
• Acute narrow-angle glaucoma
• Alcohol or other substance dependence
• Pregnancy
• History of disinhibition with BZ

Drug Interactions

• Additive effects with other sedative or hypnotic drugs
• Rate of absorption and CNS depression are both increased by alcohol
• Effects may be potentiated by phenothiazines, narcotics, barbiturates, MAOIs, and TCAs

Drug Interactions (cont.)

• CYP450 interactions
  – Note: Several BZ are oxidized by 3A4, and thus their levels will be increased by 3A4 inhibitors such as cimetidine, erythromycin, ketoconazole, or grapefruit juice
• BZ are relatively safe, and even large overdoses are rarely fatal unless taken in combination with alcohol or other drugs

Monitoring

• No special work-up is needed before starting a BZ, except for a pregnancy test in adolescent or adult females
• Adverse effects, especially sedation and disinhibition
• Tolerance and withdrawal
  – Signs and symptoms of withdrawal include: ↑ anxiety, insomnia, ↑ HR & BP, diaphoresis, tremor, hyperreflexia, seizures, delirium tremens

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Monitoring (cont.)

- Evidence of abuse, dependence, and diversion (by youth or their parents)
- Long-term use is not recommended for most children and adolescents
- With discontinuation of BZ, distinguish among:
  - Return of the original symptoms
  - Rebound increase in severity of original symptoms
  - Symptoms of physiologic withdrawal

Choosing a BZ

- Important to consider the reason for using a BZ and the desired PK profile; for example:
  - BZ with shorter $T_{1/2}$ (e.g., lorazepam) are desirable for the treatment of insomnia to minimize daytime sedation and unwanted cognitive effects
  - BZ with longer $T_{1/2}$ (e.g., clonazepam) are desirable for the treatment of anxiety, because they provide more consistent anxiolytic effects and are associated with a lower risk of withdrawal
  - Shorter onset of action is desirable for treatment of acute agitation, but this must be weighed against the duration of action (e.g., lorazepam is often used instead of diazepam, which has a shorter onset of action but a much longer $T_{1/2}$)

Pediatric Dosing of BZ

- No dosing guidelines have been established for BZ in the treatment of childhood psychiatric disorders
- In general, BZ should be titrated up slowly to minimize drowsiness and other side effects
- In general, BZ should also be tapered off slowly to avoid withdrawal, which can be dangerous
- In the treatment of anxiety, multiple daily doses are recommended to maximize effects and minimize sedation and withdrawal, even for BZ with relatively long $T_{1/2}$ (Baldessarini, 1996)

Indications and Clinical Use

- In adults, buspirone is approved for short-term (up to 4 weeks) treatment of anxiety in individuals with GAD (Health Canada and FDA)
- In children and adolescents, buspirone has no approved indications (Health Canada and FDA)
- Clinically, buspirone has been used in pediatric populations to treat anxiety

Buspirone
**Pharmacodynamics**

- **Serotonergic effects:**
  - Partial agonist or mixed agonist/antagonist at 5-HT₁A receptors
  - Predominantly agonistic activity at the presynaptic 5-HT₁A autoreceptors, which are present in high concentrations in the dorsal raphe nucleus:
    - ↑ negative feedback, which results in ↓ release of serotonin in the dorsal raphe nucleus
    - This, in turn, is thought to result in anxiolysis
  - Partial agonistic activity at the postsynaptic 5-HT₁A receptors, which are present in high concentrations in the hippocampus and cortex:
    - This may account for antidepressant effects

- **Noradrenergic effects:**
  - 1-pyrimidinylpiperazine (1-PP), the main metabolite of buspirone, has central α₂-adrenergic blocking activity
  - Blocking of presynaptic α₂-adrenergic autoreceptors ↓ negative feedback and results in ↑ noradrenergic activity in the locus ceruleus
  - This may account for buspirone’s potential usefulness as an augmentation strategy for depression and for treatment of SSRI-induced sexual dysfunction

- **Dopaminergic effects:**
  - Moderate antagonist of presynaptic D₂ autoreceptors, and thus ↑ dopaminergic neurotransmission through inhibition of negative feedback
  - Buspirone’s dopaminergic effects are probably clinically unimportant in general
  - However, in an open study of buspirone in youth with PDD, one child developed an orofacial-lingual dyskinesia after 10 months of treatment, and this resolved completely within 2 weeks of discontinuing buspirone (Buitelaar et al., 1998)

- **GABA system:**
  - No direct effects

**Pharmacokinetics**

- **Almost completely absorbed within 1 hr of oral administration**
- **Oral bioavailability is reduced, however, by substantial first-pass metabolism, which is even greater at higher doses**
- **Taking with food does not affect absorption, but ↓ first-pass metabolism**
- **>95% protein-bound**
- **Tₘₐₓ=40-90 min (children and adults)**
- **T₁/₂=2-4 hrs in adults and older children, but 1-2 hrs in children 4-6 years old (Edwards et al., 2006)**
- **Extensively metabolized to 1-PP:**
  - Pharmacologically active
  - Present in concentrations several times higher than the parent compound
  - T₁/₂=3-4 hours in children and adults
- **Cₘₐₓ of both buspirone and 1-PP is higher in children compared to adults (Salazar et al., 2001)**

- **CYP 3A4 substrate**
- **Not known to inhibit or induce any of the CYP450 systems, but this has not been well studied**
- **Excreted mostly in the urine, but also in feces**
**Efficacy: Anxiety**

- No DBPC trials of buspirone for pediatric anxiety have been published

- Simeon et al., 1994:
  - 15 children (mean age=10 years) with various anxiety disorders
  - Single-blind PBO x 2 wks, then buspirone x 4 wks
  - Dose range: 5-10 mg BID (mean=18.6 mg/day)
  - Outcome measure: CGI
  - Results: no subjects improved on PBO, and all improved on buspirone (3 "marked," 10 "moderate," 2 "minimal")

**Adverse Effects**

- Most studies of buspirone in youth report only mild side effects, which usually improve within a week

- Common side effects include:
  - Dizziness, lightheadedness
  - Headache
  - Nausea, vomiting, dyspepsia
  - Nervousness
  - Insomnia
  - Sedation
  - Agitation
  - Euphoria

**Contraindications**

- Hypersensitivity to buspirone

- Severe hepatic or renal impairment

- Concurrent MAOI

**Drug Interactions**

- 3A4 inhibitors/inducers

- Buspirone ↑ levels of haloperidol, likely because of competitive inhibition of the oxidative dealkylation of haloperidol

- MAOIs (hypertension)

**Monitoring**

- No specific medical monitoring is recommended in adults

**Dosing: General Info**

- No official guidelines for dosing in children and adolescents

- Dose BID-TID because of short T_{1/2}

- Maximum daily dose in adults: 45 mg (HC) or 60 mg (FDA)

- Studied and found to be safe in children and adolescents at doses up to 30 mg BID (Salazar et al., 2001)

- Usual optimal doses in adult clinical trials: 20-30 mg/day

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Dosing: General Info (cont.)

• May take 1-2 weeks at a given dose to achieve anti-anxiety effect (Sussman, 1994)
• Further symptom improvement may continue for at least 4 weeks at a given dose, with psychic symptoms of anxiety improving sooner than somatic symptoms (Feighner & Cohen, 1989)

Dosing: Specifics

• Adult dosing (CPS):
  – Start 5 mg BID-TID, and ↑ by 5 mg q2-3 days to a maximum of 45 mg/day
• Suggested pediatric dosing (modified slightly from Coffey, 1990):
  – Children: start 2.5-5 mg/day, and ↑ by 2.5 mg q3-4 days to a maximum of 20 mg/day
  – Adolescents: start 5-10 mg/day, and ↑ by 5-10 mg q3-4 days to a maximum of 45-60 mg/day

Indications

• Adjunctive therapy for patients with epilepsy (HC & the FDA):
  – Not approved by HC for use in children or adolescents (<18 years)
  – Approved by the FDA for use in children ≥3 years
• Treatment of postherpetic neuralgia in adults (FDA but not HC)

Gabapentin

Psychiatric Uses

• GBP has been used clinically for:
  – Mood disorders (bipolar and unipolar) in adults and children
  – Anxiety in adults and children
  – Irritability in individuals with severe neurological impairment

GBP & Pediatric Bipolar Disorder

• In most recent treatment guidelines for PBD (Kowatch et al., 2005), GBP is not included in the pharmacologic algorithm because of the lack of efficacy data in both adults and children
Pharmacodynamics

- GBP’s mechanism of action remains unclear
- Although GBP is a structural analog of GABA, it appears to lack direct GABAergic activity
- Nonetheless, GBP appears to ↑ cerebral GABA levels
- Several other effects have also been implicated:
  - GBP modulates (but does not directly block) sodium channels
  - GBP may modulate calcium channels to ↓ monoamine release
  - GBP may have anti-glutamatergic actions mediated by inhibition of glutamate synthesis
  - GBP ↑ human whole blood serotonin concentration

Pharmacokinetics: Adults

- $T_{\text{max}}=2-3$ hours
- Because of saturable absorption in the gut, GBP has nonlinear PK such that oral bioavailability ↓ with ↑ dose (Stewart et al., 1993):
  - 60% with 300 mg po TID (i.e., 540 mg bioavailable)
  - 27% with 1,600 mg po TID (i.e., 1296 mg bioavailable)
- Food has no effect on the rate or extent of GBP absorption
- <3% of GBP is bound to plasma proteins

Pharmacokinetics: Adults (cont.)

- GBP is not metabolized to a significant extent
- GBP does not induce or inhibit hepatic enzyme activity
- GBP is eliminated solely by renal excretion as unchanged drug, and can be removed from plasma by hemodialysis
- $T_{\text{1/2}}=5-7$ hrs (with normal renal function)

Pharmacokinetics: Children

- Conclusions of a study of GBP PK in children and young adults with epilepsy (Gatti et al., 2003):
  - GBP PK differences between children and adults appear to be relatively small, particularly when children ≥4 years old are considered
  - Nonetheless, on average children may need moderately higher weight-adjusted doses to reach plasma GBP concentrations comparable with those found in adults

Pharmacokinetics: Children (cont.)

- Gatti et al., 2003 (cont.):
  - Despite previous evidence that GBP has nonlinear PK, this study found that in children given doses of GBP up to 50 mg/kg/day, GBP PK were essentially linear
  - Possible explanations for the finding of GBP’s linear kinetics in children:
    - Very large dosages were not used in the study
    - Higher capacity of the intestinal active transport carrier in children

Efficacy: Adult Bipolar Disorder

- Several open trials suggested that GBP may be beneficial in the treatment of adults with bipolar disorder:
  - Young et al., 1997
  - McElroy et al., 1997
  - Schaffer & Schaffer, 1997
  - Erfurth et al., 1998
  - Knoll et al., 1998
Efficacy: Adult Bipolar Disorder (cont.)

- Pande et al., 2000:
  - DBPC trial of adjunctive GBP (900-3600 mg/day) in 117 adults with bipolar I disorder who were in a manic, hypomanic, or mixed state
  - Primary outcomes: YMRS and HAM-D
  - Results:
    - YMRS: PBO > GBP (p<0.05)
    - HAM-D: GBP = PBO
    - Secondary outcome measures: GBP = PBO

Efficacy: Adult Bipolar Disorder (cont.)

- Frye et al., 2000:
  - DBPC trial of GBP or LTG monotherapy in 31 adults with refractory bipolar or unipolar affective illness
  - Primary outcome: CGI for Bipolar Illness
  - Response rates:
    - LTG (52%) > GBP (26%) (p=0.01)
    - LTG (52%) > PBO (23%) (p=0.02)
    - GBP (26%) = PBO (23%)

Efficacy: Pediatric Bipolar Disorder

- Evidence that supports the efficacy of GBP for PBD is limited to:
  - Case reports:
    - Soutullo et al., 1998
    - Hamrin & Bailey, 2001
  - A retrospective review:
    - Ryback et al., 1997:
      - 16/18 adolescents “responded positively” to GBP; 2/18 discontinued GBP because of adverse effects

More Harm Than Good?

- Some reports have suggested that GBP may cause aggression and other behavioural problems in children:
  - Wolf et al., 1995:
    - Case report of 3 children with epilepsy and LD
  - Tallian et al., 1996:
    - Case report of 2 children with epilepsy
  - Lee et al., 1996:
    - Case series of 7 children with epilepsy, ADHD, and developmental delays
  - Khurana et al., 1996:
    - Open trial in 32 youth with epilepsy
    - 15 of these youth who also had MR and baseline behavioural problems exhibited worsening behaviour with GBP

Efficacy: Adult Anxiety Disorders

- Pande et al., 1999:
  - DBPC trial of 69 adults with social phobia
  - GBP > PBO (p<0.05)
- Pande et al., 2000:
  - DBPC trial of 103 adults with panic disorder
  - GBP = PBO overall
  - Post hoc analysis revealed GBP > PBO (p=0.04) for the more severely ill patients
- De-Paris et al., 2003:
  - Open study suggesting that GBP may be beneficial for the treatment of performance anxiety in adults

Efficacy: Pediatric Anxiety

- Evidence that supports the efficacy of GBP for pediatric anxiety is limited to a case report (Durkin, 2002):
  - 2 adolescents with school refusal and a variety of longstanding psychiatric symptoms
  - Both adolescents appeared to benefit from GBP and were able to return to school or go to work
Efficacy: Irritability in Neurologically Impaired Children

- Hauer et al., 2007:
  - Case series of 9 severely neurologically impaired, nonverbal youth (9 months to 22 years old) treated with GBP for recurrent irritability
  - Caregivers reported marked improvement in all patients after GBP treatment
  - The authors conclude that visceral hyperalgesia may be a source of unexplained irritability in neurologically impaired children, and symptoms may improve with GBP because of its benefit for neuropathic pain

Adverse Effects

- GBP is generally safe and well tolerated, but common adverse effects include:
  - Somnolence, fatigue
  - Nausea, vomiting
  - Ataxia
  - Dizziness
  - Nystagmus
  - In children:
    - Emotional lability
    - Behavioural problems, including aggression and hyperactivity
    - Impaired concentration
  - In addition, as with all anticonvulsants, GBP is associated with a small ↑ risk of suicidality (FDA Warning, Dec. 2008)

Contraindications

- Hypersensitivity to GBP
- Pregnancy (relative contraindication)

Drug Interactions

- GBP ↓ hydrocodone levels; hydrocodone ↑ GBP levels
- Morphine ↑ GBP levels
- Naproxen ↑ absorption of GBP
- Aluminum- and magnesium-based antacids (e.g., Maalox) ↓ GBP bioavailability by up to 20%:
  - Therefore, GBP should be taken ≥2 hours after taking these antacids

Pre-treatment Work-up

- Medical history & physical exam
- No routine baseline labs are necessary (besides pregnancy test for menstruating females)
- For patients with impaired renal function, creatinine clearance should be assessed
Monitoring
- Evidence of suicidality or depression (as with all anticonvulsants in all age groups)
- GBP levels are not routinely monitored
- No routine lab monitoring is required
- In patients with renal impairment, monitoring of renal function is indicated

Dosing Comments
- Because of its short T½, GBP should be dosed TID, and the maximum time between doses should be ≤12 hours
- Given that GBP is eliminated solely by renal excretion as unchanged drug, dosing adjustments are recommended for patients with renal impairment (see CPS for details)
- If patients cut a 600 or 800 mg tablet in order to take a half-tablet, they should take the unused half-tablet as the next dose (half-tablets not taken within several days of cutting should be discarded)

Dosing for Epilepsy
- Adults and adolescents (CPS & PDR):
  - Start 300 mg po TID
  - Depending on response and tolerance, consider titrating up
  - Usual dose range: 900-1800 mg/day
  - Maximum dose: 3600 mg/day

Dosing for Epilepsy (cont.)
- Children aged 3-12 years (PDR):
  - Start 10-15 mg/kg/day, and then titrate up over 3 days
  - Usual dose range in children ≥5 years:
    - 25-35 mg/kg/day
  - Usual dose range in children 3-4 years:
    - 40 mg/kg/day
    - Note that this is higher than for older children
  - Maximum dose:
    - 50 mg/kg/day

Modafinil

Dosing for Adult Bipolar Disorder
- Dosing is unclear, as efficacy at any dose has not been established
- Dosing used in the study by Pande et al., 2000:
  - GBP “dosed flexibly” between 900 and 3600 mg/day (details not described)
- Dosing used in the study by Frye et al., 2000:
  - Start 900 mg/day
  - Titrated to 1500 mg/day by end of week 1
  - Titrated to 2700 mg/day by end of week 2
  - Titrated to 3600 mg/day by end of week 3
  - Titrated to 4200 mg/day by end of week 4
  - Titrated to 4800 mg/day by end of week 5-6
Indications and Clinical Use

- No approved pediatric indication in either Canada or the U.S.
- Indicated in adults for excessive daytime sleepiness associated with narcolepsy, obstructive sleep apnea, or shift work sleep disorder (Health Canada and FDA)
- Clinically, modafinil is sometimes used for ADHD after multiple other agents have failed

Pharmacodynamics

- Modafinil is a CNS stimulant, but its mechanism of action is poorly understood
- It has been thought that modafinil’s mechanism of action differs from that of MPH and amphetamine, which ↑ DA in the brain, and that its effects involve hypocretin, histamine, epinephrine, GABA, and glutamate (Lin et al., 1996; Scammell et al., 2000)
- However, there is mounting evidence that modafinil’s mechanism of action does involve DA, and a recent pilot study found that modafinil blocked DA transporters and ↑ DA levels in the human brain (Volkow et al., JAMA, 2009)

Pharmacokinetics

- Adults:
  - $T_{max}=3$ hrs, $T_{1/2}=10$ hrs
  - Taking with food has no effect on overall bioavailability, but may delay absorption by about 1 hour
  - Moderately bound (60%) to plasma protein
  - Mainly metabolized in the liver, partly by CYP 3A4, to two inactive metabolites
  - Modafinil may induce metabolizing enzymes, especially CYP 3A4 as well as CYP 1A2 and CYP 2B6
  - Modafinil may inhibit CYP 2C9 and CYP 2C19

Efficacy: ADHD

- Negative DBPC trials:
  - Cephalon, Inc., unpublished (N=113; adults)

- Positive but small DBPC trials:
  - Taylor & Russo, 2000 (N=22; adults)
  - Rugino & Samsock, 2003 (N=24; children)
  - Turner et al., 2004 (N=20; adults)
  - Kahbazi et al., 2009 (N=46; children & adolescents)

Efficacy: ADHD (cont.)

- Positive and large DBPC trials:
  - Biederman et al., 2005 (N=248; children & adolescents)
  - Swanson et al., 2006 (N=190; children & adolescents)
  - Greenhill et al., 2006 (N=200; children & adolescents)
  - Biederman et al., 2006 (N=248; children)

Efficacy: ADHD (cont.)

- Main findings of the first 3 studies on the previous slide:
  - Mean dose $>360$ mg/day
  - Response rate: modafinil 37%-52% vs. placebo 17-18%
  - Effect size: 0.6-0.8 ("medium" to "large")
  - Modafinil was generally well tolerated
Efficacy: ADHD (cont.)

- Biederman et al., 2006:
  - 4 dosing regimens compared in children aged 6-13 years:
    - 300 mg QAM
    - 100 mg QAM, 200 mg Qnoon
    - 200 mg QAM, 100 mg Qnoon
    - 200 mg BID (for children >30 kg)
  - Placebo
  - Overall, modafinil > PBO
  - 300 mg QAM provided the most consistent improvement in symptoms
  - All dosing regimens were well tolerated

Meta-analysis: Wang et al., 2017

- Includes 5 DBPC trials of modafinil in children & adolescents:
  - Biederman et al., 2005; Swanson et al., 2006; Greenhill et al., 2006; Biederman et al., 2006; Kahbazi et al., 2009
- Modafinil > PBO for ADHD symptoms:
  - ADHD-RS-IV Home: Effect size = 0.77
  - ADHD-RS-IV School: Effect size = 0.71
- Modafinil was associated with a significantly higher incidence of ↓ appetite and insomnia
- Dropout rate due to adverse events did not differ significantly between the modafinil and PBO groups

Adverse Effects

- Insomnia*†
- Headache*
- ↓ appetite*†
- Weight loss*
- Abdominal pain
- Nausea
- Somnolence

*Most common
†Usually resolves with continued treatment

Risk of Serious Skin and Other Hypersensitivity Reactions

- In pediatric clinical trials of modafinil, the incidence of rash resulting in discontinuation was 0.8% (13/1,585), including 1 case of possible Stevens-Johnson syndrome and 1 case of apparent multi-organ hypersensitivity reaction
- No such cases were observed among 380 pediatric patients who received placebo
- No serious skin rashes have been reported in adult clinical trials of modafinil (4,264 subjects)

Risk of Psychiatric Adverse Events

- In adult clinical trials, psychiatric symptoms resulting in treatment discontinuation and reported more often with MOD than PBO were: anxiety (1%), nervousness (1%), insomnia (<1%), confusion (<1%), agitation (<1%), and depression (<1%)
- In clinical trials of youth with ADHD:
  - Psychosis, mania, or SI were reported in <1% of patients treated with MOD and none treated with PBO
- In clinical trials of youth with narcolepsy or OSAHS:
  - No reports of psychosis, mania, or SI
  - Aggression and violent behaviour were reported in 1% of patients treated with MOD and none treated with PBO

Health Canada Warning (December 2007)

- Modafinil can cause life-threatening skin and other serious hypersensitivity reactions:
  - Severe cutaneous adverse reactions (SCARs), including Toxic Epidermal Necrolysis (TEN), Stevens-Johnson Syndrome (SJS), and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), have occurred in adults and children using modafinil.
  - Angioedema, anaphylactic reaction, and multi-organ hypersensitivity reactions, including at least one fatality, have also been reported with the use of modafinil.
- Modafinil is not approved for use in pediatric patients for any indication.
- Modafinil can cause psychiatric symptoms.
Other Potential Risks

• The FDA has also raised concern about the risk of liver toxicity, but specific data are not easily available

• Modafinil’s potential for abuse is controversial (Kruszewski et al., 2006; Kruszewski et al., 2007)

Contraindications

• Hypersensitivity to modafinil

• “Patients in agitated states” (CPS)

• “Patients with severe anxiety” (CPS)

• Presence of the HLA-B*1502 allele (see “Carbamazepine and Other Anticonvulsants” handout for further details)

Drug Interactions

• Methylphenidate and dextroamphetamine: – Absorption of modafinil may be delayed by about an hour

• Warfarin: – Although no significant interaction has been found, more frequent monitoring of PT/INR is advised

• MAOIs: – Interaction studies have not been performed, but be cautious

Drug Interactions (cont.)

• CYP 3A4 inducers: – E.g., carbamazepine, phenobarbital, rifampin – May ↓ modafinil levels

• CYP 3A4 substrates: – E.g., OCP, cyclosporine – Levels of these drugs may be ↓ by modafinil

• CYP 2C19/2C9 substrates: – E.g., diazepam, propranolol, phenytoin – Levels of these drugs may be ↑ by modafinil

Pre-treatment Work-up & Monitoring for Serious Rashes

• Consider HLA-B*1502 genotyping in individuals of Asian ancestry (see “Carbamazepine and Other Anticonvulsants” handout for further details)

• Modafinil should generally be discontinued at the first sign of rash, unless it is clearly not drug-related:
  – Almost all cases of serious rash associated with modafinil occurred within 1-5 weeks of treatment initiation, but isolated cases have been reported after prolonged treatment (e.g., 3 months)
  – Although benign rashes can occur with modafinil, it is not possible to predict reliably which rashes will prove to be serious

Other Monitoring

• Response and adverse effects (preferably using child/parent and teacher rating scales)

• HR and BP

• Height and weight on a growth chart
Dosing

- In Canada, modafinil is available in 100 mg tablets under the trade name Alertec.
- As a frame of reference, modafinil dosing for adults with excessive daytime sleepiness is as follows:
  - Usual starting dose: 100 mg BID (morning & noon) or 200 mg QAM
  - Maximum dose: 400 mg/day, 300 mg/dose

Dosing (cont.)

- When treating children and adolescents for ADHD:
  - Modafinil may be dosed QAM or BID (morning & noon), although the study by Biederman et al., 2006, suggests that QAM dosing is more effective.
  - Initial response may occur within a couple of weeks, but full response may take several weeks to a couple of months.

Suggested Titration Schedule

- Start modafinil 50-100 mg po qam
- ↑ weekly by 50-100 mg up to a maximum of 400 mg/day according to clinical response and tolerability
- Maximum dose used in published studies: 425 mg/day (85 mg tablet x 5 QAM)
- Studies suggest that, regardless of body weight, most patients will benefit from titrating modafinil towards the maximum dose (Biederman et al., 2005; Greenhill et al., 2006)
- For children <30 kg, however, consider stopping at a maximum dose of 300 mg/day (Biederman et al., 2006) or 340 mg/day (Swanson et al., 2006)

Monoamine Oxidase Inhibitors

Use (or Non-Use) of MAOIs in Child Psychiatry

Because MAOIs are associated with serious adverse effects and food and drug interactions, they have not been well studied in children and adolescents, and their use in this population is generally not recommended.

Pharmacodynamics

- Inhibit the activity of monoamine oxidase (MAO), which metabolizes 5-HT, NE, and DA in the presynaptic neuron.
- Consequently, the levels of intracellular 5-HT, NE, and DA ↑, resulting in ↑ release of these neurotransmitters.
- 2 types of MAO:
  - MAO-A: preferentially deaminates 5-HT and NE
  - MAO-B: preferentially deaminates phenylethylamine and benzylamine
  - Both deaminate DA and tyramine.
Pharmacodynamics (cont.)

- MAO-A is found primarily in the gut and sympathetic nerve terminals; it accounts for 20% of CNS MAO
- MAO-B is found primarily in the CNS; it accounts for 80% of CNS MAO
- MAOIs can be classified according to:
  - Selectivity for MAO-A or MAO-B
  - Reversibility of the MAO-drug bond

Specific Drugs

- Irreversible, non-selective inhibition:
  - Phenelzine
  - Tranylcypromine
  - Isocarboxazid (not available in Canada)

- Reversible, selective inhibitor of MAO-A (RIMA):
  - Moclobemide

- Irreversible, selective inhibitor of MAO-A:
  - Clorgyline

- Irreversible, selective inhibitor of MAO-B:
  - Selegiline (becomes nonselective at higher doses)

Specific Drugs (cont.)

- In this seminar, we will focus mainly on phenelzine (PZ) and tranylcypromine (TC)
- Isocarboxazid, selegiline, and clorgyline are not available in Canada
- There is one small (N=20) DBPC trial of moclobemide in children and adolescents with MDD, and it was negative (Avci et al., 1999)

Pharmacokinetics

- PZ and TC are both rapidly absorbed
- Both have short $T_{1/2}$:
  - PZ: 1.5-4 hrs (adults)
  - TC: 1.5-3 hrs (adults)
- The liver appears to be the primary site of metabolism, but MAOI metabolism is poorly understood
- TC is a 2C19 inhibitor

Pharmacodynamic vs. Pharmacokinetic Effects

- PZ and TC have enduring effects beyond their $T_{1/2}$ because of the irreversibility of their enzyme inhibition
- With discontinuation, PZ and TC are usually cleared within 24 hrs, but the regeneration of MAO may take as long as 1-2 weeks.
- The maximal inhibition of MAO typically requires several days to weeks of treatment

Efficacy: MDD

- Ryan et al., 1988:
  - Chart review of 23 adolescents with MDD who had partial or no response to TCAs, and were subsequently treated with PZ or TC alone or in combination with a TCA
  - 17/23 had a “fair to good” antidepressant response, but 4 responders were noncompliant with the MAOI diet, and so only 13 continued on the medication
  - 7/23 had purposeful or accidental dietary noncompliance
Efficacy: ADHD

- Zametkin et al., 1985:
  - In a controlled study, PZ and clorgyline were as effective and well tolerated as dextroamphetamine
- Rapoport et al., 1985:
  - In a crossover study, selegiline was less efficacious than dextroamphetamine
- Zametkin & Rapoport, 1987:
  - Selegiline administered to 14 hyperactive children had relatively little therapeutic effect
- Jankovic, 1993:
  - In an open study of selegiline for children with Tourette syndrome (TS) & ADHD, the vast majority reported improvement in ADHD symptoms with no serious adverse events
- Feigin et al., 1996:
  - Controlled trial of low-dose selegiline in children with TS & ADHD did not demonstrate improvement in ADHD symptoms

Adverse Effects

- Orthostatic hypotension (dose-related)
- Sedation (PZ>TC)
- Insomnia, activation (TC>PZ)
- Edema
- Weight gain
- Dry mouth
- Sexual dysfunction
- Hepatitis (rare)
- Leukopenia (rare)
- Paresthesia:
  - Due to MAOI-induced pyridoxine deficiency, and it responds to oral pyridoxine supplementation

Severe Risks

- Dangerous in overdose:
  - Severe autonomic and CNS instability
- Serotonin syndrome
- Hypertensive-adrenergic crisis

Severe Risks (cont.)

- Serotonin syndrome:
  - Associated with ingestion of serotonergic drugs
  - Characterized by mental status changes, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, and incoordination
- Hypertensive-adrenergic crisis:
  - Associated with ingestion of dietary tyramine and other amines (normally deaminated in the gut, mainly by MAO-A) and sympathomimetic drugs
  - In addition to hypertension, the clinical presentation may include headache, diaphoresis, mydriasis, neuromuscular irritability, cardiac arrhythmias, stroke, and MI

Contraindications

- Hypersensitivity to the MAOI
- Hypertension
- Cerebrovascular or cardiovascular disorders
- Recurrent headaches
- Liver disease
- Blood dyscrasias
- Known or suspected pheochromocytoma
- Unwillingness or inability to adhere to dietary restrictions (i.e., to avoid foods containing tyramine, such as aged cheeses and meats, red wine, and beer)
Drug Interactions

Risk of serotonin syndrome with drugs that inhibit serotonin reuptake:

- SSRIs
- Venlafaxine
- TCAs
- Meperidine (Libby Zion case)
- Dextromethorphan
- Propoxyphene

Drug Interactions (cont.)

Risk of hypertensive-adrenergic crisis with sympathomimetics:

- Amphetamines
- Methylphenidate
- Dopamine
- Ephedrine
- Epinephrine
- Isoproterenol

- Metaraminol
- Oxymetazoline
- Phenylephrine
- Phenylpropanolamine
- Pseudoephedrine
- Caffeine

Drug Interactions (cont.)

Other drug interactions:

- Oral hypoglycemics (further lowering of serum glucose)
- 2C19 substrates are inhibited by TC
- Bupropion (hypertensive crisis)
- L-dopa (hypertensive crisis)
- Sumatriptan (a serotonin agonist that is also metabolized by MAO)
- Tryptophan

Monitoring

- Concomitant medications (including OTC drugs and complementary remedies)
- Dietary adherence
- BP (could be low or high)
- Some authorities recommend EKG and LFT monitoring
- Suicidality and risk of overdose

Choosing an MAOI: PZ or TC?

- PZ has been better studied in adults but is associated with a greater incidence of adverse effects (especially weight gain, sedation, dry mouth, and sexual dysfunction)
- Although hepatotoxicity is rare with both PZ and TC, the risk of serious or fatal hepatotoxicity is greater with PZ
- Slightly higher risk of hypertensive crisis with TC, but MAO function returns to normal more quickly when TC is discontinued
- Bottom line: Can start with either PZ or TC, but because of side effect profiles, would suggest starting with TC unless patient is very concerned about insomnia

Dosing

- No dosing guidelines for MAOIs in children and adolescents are available
- Adult dosing:
  - Phenelzine
    - Start 15 mg BID-TID
    - ↑ by 15 mg/week to 45-60 mg/day and maximum of 90 mg/day
  - Tranylcypromine
    - Start 10 mg BID
    - If no response after a few weeks, ↑ by 10 mg/week to 30 mg/day and maximum of 40 mg/day (although higher doses are sometimes used)

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Dosing (cont.)
• Therapeutic response is often not evident for 2-4 weeks, and may take as long as 8 weeks
• When discontinuing an MAOI, the medication should be tapered over a week or more to avoid withdrawal symptoms (rare incidents of delirium with abrupt discontinuation have been reported)

Starting and Stopping
• After an MAOI is tapered off, wait at least 2 weeks before discontinuing both dietary and drug restrictions
• With the exception of fluoxetine, wait at least 2 weeks after stopping another antidepressant before starting an MAOI
• Wait at least 5 weeks after stopping fluoxetine before starting an MAOI

Topiramate

Indications
• TPM is approved for:
  – Initial monotherapy for epilepsy in adults and children (≥6 years per HC, ≥10 years per the FDA)
  – Adjunctive therapy for epilepsy in adults and children (≥2 years per HC and the FDA) who do not have an adequate response to conventional therapy
  – Prophylaxis of migraine headache in adults (HC and the FDA)

Psychiatric Uses
• TPM has been used clinically for:
  – Bipolar disorder in adults and children
  – “Disorders of impulsivity”:
    • Alcohol dependence (Johnson et al., 2003), bulimia nervosa (Hoopes et al., 2003), binge eating (McElroy et al., 2003), pathological gambling, and borderline personality disorder
  – Weight reduction in patients taking psychotropic medications that cause weight gain, especially atypical antipsychotics
  – Tics in Tourette syndrome

TPM and Pediatric Bipolar Disorder
• In most current treatment guidelines for PBD (Kowatch et al., 2005), TPM is not included in the pharmacologic algorithm because of the lack of efficacy data in both adults and children
Pharmacodynamics

• TPM’s mechanism of action remains unclear, but it has several effects that have been implicated:
  – GABA-ergic effects:
    • Positively modulates GABA<sub>A</sub> receptors
    • ↑ cerebral GABA levels
  – Anti-glutamatergic effects:
    • Blocks kainate and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors
    • Blocks sodium channels
    – Weakly inhibits carbonic anhydrase type II (CA-II) and type IV (CA-IV) isoenzymes

Pharmacokinetics

• Adults:
  – The pharmacokinetics of TPM are linear over a single dose range of 100-400 mg
  – TPM is rapidly and well absorbed, with an oral bioavailability of about 80% and T<sub>max</sub>=2-3 hours
  – Taking TPM with food has no clinically significant effect on its bioavailability
  – Plasma protein binding: 13-41%

Pharmacokinetics (cont.)

• Adults (cont.):
  – TPM is not extensively metabolized (about 20%)
  – 6 metabolites formed through hydroxylation, hydrolysis, and glucuronidation have been identified, and none has anticonvulsant activity
  – In the absence of concomitant hepatic enzyme inducers, about 70% of a TPM dose is excreted unchanged in the urine
  – Mean T<sub>1/2</sub>=21 hours (it takes 4-8 days to reach steady-state plasma concentrations)

Pharmacokinetics (cont.)

• Children:
  – TPM clearance is approximately 50% higher in children compared with adults
  – Steady-state plasma TPM concentrations for the same weight-adjusted dose are expected to be one-third lower in children compared with adults

Efficacy: Adult Bipolar Disorder

• Kushner et al., 2006:
  – Report of 4 multicenter DBPC trials of TPM monotherapy for acute mania in adults with bipolar I disorder
  – 2 of the 4 trials also included a group randomized to Li
  – TPM dose: 200, 400, or 600 mg/day
  – Core study duration in all 4 trials was 3 weeks, but 3 of the trials also had 9-week double-blind extensions
  – In each of the core 3-week studies, the primary efficacy outcome measure was mean YMRS change from baseline

Kushner et al., 2006: Efficacy Results

• Changes in YMRS score were not significantly different for TPM vs. PBO:
  – In each of the 4 studies considered individually, in all 4 pooled together, at the end of 3 weeks, and at the end of 12 weeks
  – In the 2 studies that included a Li group, improvements in YMRS were significantly greater for Li vs. both TPM and PBO:
    – In each of the 2 studies considered individually, in both pooled together, at the end of 3 weeks, and at the end of 12 weeks
  – In the pooled analysis, PBO > TPM on the:
    – MADRS (Montgomery-Asberg Depression Rating Scale)
    – BPRS (Brief Psychiatric Rating Scale)
Kushner et al., 2006:
Adverse Event Results

- In the pooled analysis:
  - Adverse events occurring more frequently (≥3% higher incidence rate) with TPM than PBO:
    - Paresthesia, dry mouth, ↓ appetite, weight loss
  - Suicidality:
    - SREs during the core 3-week studies: TPM=7/656 (1.1%); PBO=3/429 (0.7%, all were SI); Li=0/227 (0%)
    - 1 patient on TPM completed suicide

Efficacy: PBD

- 3 case reports suggest that TPM was beneficial for pediatric mania:
  - Davanzo et al., 2001 (TPM was discontinued because of significant cognitive deterioration)
  - Pavuluri et al., 2002 (“TPM Plus Risperidone for Controlling Weight Gain and Symptoms in Preschool Mania”)
  - Basu et al., 2004
- 2 chart reviews suggest that adjunctive TPM may be beneficial for PBD:
  - Delbello et al., 2002 (outpatients)
  - Barzman et al., 2005 (inpatients)

Efficacy: PBD – cont.

- 1 open study examining role of adjunctive TPM for PBD:
  - Wozniak et al., 2009, 8 week trial
  - olanzapine + TPM grp and olanzapine grp both had statistically significant drop in YMRS (p=.04)
  - the olanzapine + TPM grp had significantly less wt gain (2.6 +/- 3.6 kg vs.5.3 +/- 2.1 kg)
  - cholesterol levels significantly higher in the olanzapine + TPM grp at end pt (p=.009)! (blood tests were not ‘fasting’)

Delbello et al., 2005 (cont.)

- For ethical reasons, the study was discontinued early when adult mania trials with TPM failed to show efficacy (Kushner et al., 2006)
- Consequently, for the primary efficacy analysis, the study’s power is only 43%:
  - In other words, if a difference between TPM and PBO actually exists, the probability the study could detect it is only 43%

DBPC Trial of TPM for PBD

- Delbello et al., 2005:
  - 4-week DBPC pilot study of TPM monotherapy for acute mania in 56 children and adolescents (mean age=13.8 years) with bipolar I disorder
  - Primary efficacy outcome measure: YMRS
  - TPM target doses: 200, 300, or 400 mg/day

Delbello et al., 2005 (cont.)

- Results:
  - Reduction in mean YMRS score using LOCF was not significantly different (p=0.15) between TPM (-9.7) and PBO (-4.7)
  - Although the difference was not statistically significant, the estimated effect size was 0.51 (“medium”)
  - Some post hoc analyses suggested that TPM was superior to PBO
- Adverse effects:
  - Only ↓ appetite and nausea were more common with TPM compared with PBO
Efficacy: Impulse Control Disorders in Youth

- Barzman & Delbello, 2006:
  - Case series of 9 hospitalized youth (10-14 years old) with PBD and a disruptive behaviour disorder who were treated with adjunctive TPM
  - 6/9 (67%) responded with good tolerability

- Dolengevich Segal et al., 2006:
  - Open trial of TPM in 11 children and adolescents with a variety of "impulsive behavioural disorders"
  - Significant improvements were found on the Barrat Impulsivity Scale

Efficacy: Prader-Willi Syndrome

- Smathers et al., 2003:
  - Open trial of TPM in 8 children and adolescents with PWS
  - In 1 patient, TPM was discontinued because of parental perception of no improvement
  - In the other 7 patients, improvements were noted:
    - Positive change in mood
    - ↓ aggressive behaviour
    - ↓ self-abusive behaviour (skin picking)
    - ↓ compulsive-eating behaviour
    - ↓ weight gain, or weight loss

Common Adverse Effects

- Dizziness
- Ataxia
- Speech problems
- Psychomotor slowing
- Diplopia and other visual changes
- Paresthesias
- Somnolence, fatigue
- Nausea
- Diarrhea
- Dry mouth
- Emotional lability

Common Adverse Effects (cont.)

- Cognitive impairment (e.g., attention, memory, psychomotor speed, verbal fluency, language comprehension, arithmetic):
  - Martin et al., 1999 (healthy young adults)
  - Davanzo et al., 2001 (case report of a child with bipolar disorder, ADHD, ODD, and borderline IQ)
  - Lee et al., 2006 (adults and some adolescents with epilepsy)
  - Blum et al., 2006 (adults with epilepsy)
  - Aarsen et al., 2006 (obese children without epilepsy)
  - Kang et al., 2007 (children with epilepsy)

Common Adverse Effects (cont.)

- Hyperchloremic, non-anion gap metabolic acidosis:
  - ↓ serum bicarb without respiratory alkalosis
  - Usually mild-moderate (avg ↓ in serum bicarb of 4 mmol/L)
  - Caused by TPM's inhibition of renal carbonic anhydrase
  - Dose-related and generally occurs early in treatment
  - Can cause hyperventilation, cardiac arrhythmias, and stupor
  - If chronic, can ↓ growth, cause osteomalacia (rickets) and osteoporosis, and ↑ risk of nephrolithiasis and nephrocalcinosis
  - Adults: 32% with TPM 400 mg/day, including 3% with a marked ↓ in serum bicarb (CPS)
  - Children and adolescents: 67% with TPM 6 mg/kg/day, including 11% with a marked ↓ in serum bicarb (CPS)

Common Adverse Effects (cont.)

- Appetite suppression and weight loss:
  - Generally early in treatment
  - In clinical trials, 9% of children treated with TPM experienced weight loss, but 96% of these had resumption of weight gain (CPS)

- Hypokalemia:
  - In a small study, 3/11 subjects treated with TPM developed K<3.6 mEq/L (CPS)
Rare but Serious Adverse Effects

- Suicidality
- Acute myopia with secondary angle closure glaucoma (typically within 1 month of starting TPM)
- Hyperammonemia with or without encephalopathy
- Nephrolithiasis (1-1.5% of adults)
- Oligohydrosis and hyperthermia:
  - Reports have mainly involved children
  - Some cases have been fatal

Contraindications

- Hypersensitivity to TPM
- Pregnancy (relative contraindication)

Drug Interactions: AED’s

<table>
<thead>
<tr>
<th>AED Co-administered</th>
<th>AED Concentration</th>
<th>Topiramate Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Primidone</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>NC or ↑ dose up to 400 mg/day</td>
<td>↑ 15% increase</td>
</tr>
</tbody>
</table>

* = Plasma concentration increased 15% in some patients, generally based on a b.i.d. during regimen of phenytoin.
*↑ = The equilibrium is an active metabolite of carbamazepine.
NC = No change in plasma concentration.
AED = Antiepileptic drug.
NC = Not Changed.
TPM = Topiramate

Reference: www.pdr.net

Drug Interactions: Psychotropics

- TPM (200 mg/day) ↓ Li levels by 20%
- TPM (200 mg/day) ↓ risperidone levels by 25%
- TPM ↑ amitriptyline levels

- Potential for cognitive or other neuropsychiatric adverse effects when TPM is combined with alcohol or other CNS depressants

Drug Interactions: Other

- TPM may ↓ levels of oral contraceptives
- The combination of TPM with other carbonic anhydrase inhibitors ↑ the risk of nephrolithiasis as well as oligohydrosis and hyperthermia
- Hydrochlorothiazide ↑ TPM levels, and the combination ↑ the risk of hypokalemia compared with either medication given alone
- TPM ↑ metformin levels; metformin ↑ TPM levels
- TPM ↑ glyburide and pioglitazone levels
- TPM ↓ digoxin levels

Pre-treatment Work-Up

- Medical history & physical exam, including weight & height
- Advise adequate hydration to reduce risk of:
  - Nephrolithiasis
  - Complications from oligohydrosis during exercise or in hot weather
- Labs:
  - Electrolytes (especially serum bicarbonate, chloride, and potassium)
  - Pregnancy test for menstruating females
Monitoring

- Weight and height

- Evidence of suicidality or depression (as with all anticonvulsants in all age groups)

- Evidence of ↓ sweating and ↑ body temperature, especially in hot weather

Monitoring (cont.)

- TPM levels are not routinely monitored

- “Periodic” (CPS & PDR) serum bicarbonate:
  - Consider monthly for 3 months, then at 6 months, then q3-6 months thereafter
  - If metabolic acidosis is detected, consider ↓ or discontinuing TPM, or treating with alkali

- Given potential risk of hypokalemia, suggest also monitoring K along with serum bicarbonate

Dosing

- HC dosing recommendations for TPM monotherapy in adults and children (≥6 years) with epilepsy:
  - Start 25 mg po QHS for 1 week
  - Then ↑ to 25 mg po BID for 1-2 weeks
  - Then ↑ to 50 mg po BID (initial target dose) for at least 2 weeks
  - If doses >100 mg/day are necessary, TPM may be ↑ weekly by 50 mg/day to a max of 400 mg/day

Dosing (cont.)

- Dosing schedule used in DBPC trial of TPM for PBD by Delbello et al. (2005):
  - Start 50 mg/day
  - Children:
    • Over 5 days titrate TPM, as tolerated, to target dose determined by weight:
      - 20-29.9 kg: 200 mg/day
      - 30-39.9 kg: 300 mg/day
      - ≥40 kg: 400 mg/day
  - Adolescents:
    • Over 5 days titrate TPM, as tolerated, to 400 mg/day regardless of weight

Most Commonly Used TCAs

- Secondary amines:
  - Nortriptyline (NT)
  - Desipramine (DMI)

- Tertiary amines:
  - Imipramine (IMI)
  - Clomipramine (CMI)
  - Amitriptyline (AMI)
Pediatric Indications

- Health Canada:
  - NT: depression in individuals ≥6 years
  - DMI: not approved for use in children or adolescents
  - IMI: language is vague, but it appears to be approved for depression in adolescents as well as adults
  - CMI: depression and OCD in individuals ≥10 years
  - AMI: depression in individuals ≥12 years

Pediatric Indications (cont.)

- FDA:
  - NT: not approved for use in individuals <18 years
  - DMI: not approved for use in individuals <18 years
  - IMI: depression in individuals ≥13 years; enuresis in individuals ≥6 years
  - CMI: OCD in individuals ≥10 years
  - AMI: depression in individuals ≥13 years

Clinical Use in Child Psychiatry

- Use of TCAs in child psychiatry is limited because the risks and side effects often outweigh the potential benefits
- Most common uses of TCAs in child psychiatry:
  - OCD (CMI after at least 2 SSRIs have failed)
  - ADHD (after multiple other agents have failed)
- TCAs are also used occasionally for refractory...
  - Anxiety disorders
  - Depressive disorders
  - Enuresis

Pharmacodynamics

- Block presynaptic reuptake of neurotransmitters, mainly NE and 5-HT
- Desipramine is mostly noradrenergic
- Clomipramine is mostly serotonergic

Pharmacokinetics

- Tertiary amines are demethylated (by CYP 1A2, 2C19, 3A4) to secondary amines:
  - IMI is demethylated to DMI
  - AMI is demethylated to NT
- Secondary amines undergo hydroxylation (by CYP 2D6) and then glucuronidation before being excreted in the urine

Pharmacokinetics (cont.)

- Children tend to be more rapid metabolizers than adults, resulting in shorter elimination half-lives
- Remember that slow 2D6 metabolizers (7-10% of whites) will have higher drug levels
- Overall, there is marked inter-individual variability in the pharmacokinetics of TCAs
Pharmacokinetics (cont.)

<table>
<thead>
<tr>
<th>Adults</th>
<th></th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{max}$ (hrs)</td>
<td>$t_{1/2}$ (hrs)</td>
<td>$T_{max}$ (hrs)</td>
</tr>
<tr>
<td>AMI</td>
<td>2-12</td>
<td>10-50</td>
</tr>
<tr>
<td>IMI</td>
<td>2-5</td>
<td>5-25</td>
</tr>
<tr>
<td>CMI</td>
<td>2</td>
<td>20-50</td>
</tr>
<tr>
<td>NT</td>
<td>2-8</td>
<td>18-56</td>
</tr>
<tr>
<td>DMI</td>
<td>?</td>
<td>12-24</td>
</tr>
</tbody>
</table>

Efficacy: ADHD

- At least 31 studies (19 controlled, 12 open) have evaluated TCAs for ADHD in children and adolescents (n=1064) as well as adults (n=78)
- Almost all published studies have reported at least moderate improvement
- Effect size: "medium" to "large" (not quite as good as stimulants, but comparable to atomoxetine and $\alpha_2$ agonists)
- A patient with ADHD who does not respond to one TCA may still respond to another

Efficacy: ADHD (cont.)

- Otasowie et al., 2014:
  - Cochrane review and meta-analysis of TCAs for ADHD in children and adolescents
  - Included 6 placebo-controlled trials (4 DMI, 1 DMI & CMI, 1 NT) with total n=216
  - Quality of evidence was "low" to "very low"
  - Main finding was that TCAs, particularly DMI, improved ADHD symptoms with an effect size that was "moderate-to-large"
  - Most adverse events were mild, and none serious
  - However, the effect of TCAs on the cardiovascular system remains an important clinical concern

Efficacy: OCD

- Geller et al., 2003:
  - Meta-analysis of 12 studies (1044 subjects in total) of fluoxetine, fluvoxamine, paroxetine, sertraline, and clomipramine for pediatric OCD
  - Each medication examined was significantly better than placebo or comparator treatments
  - Overall effect size for medication was 0.46 ("medium"), equaling a difference of about 4 points (out of 40) on the CY-BOCS between active treatment and placebo

Geller et al., 2003 (cont.)

- All SSRIs were comparably effective
- Clomipramine was significantly superior to each of the SSRIs
- Nonetheless, the authors do NOT recommend clomipramine as the first-line medication for pediatric OCD, as it is associated with more frequent and serious adverse effects, particularly cardiac arrhythmias

Efficacy: Depression

- Negative DBPC trials of TCAs in youth:
  - Kramer et al., 1981 (AMI)
  - Petti et al., 1982 (IMI)
  - Kashani et al., 1984 (AMI)
  - Preskorn et al., 1987 (IMI; results equivocal)
  - Geller et al., 1989 (NT)
  - Geller et al., 1990 (NT)
  - Hughes et al., 1990 (drugs studied?)
  - Boulos et al., 1991 (DMI)
  - Geller et al., 1992 (NT)
  - Kutcher et al., 1994 (DMI)
  - Puig-Antich et al., 1987 (IMI)
  - Klein et al., 1998 (DMI)
  - Birmaher et al., 1998 (AMI)
  - Oden et al., 1998 (AMI)
  - Kye et al., 1996 (AMI; CGI showed benefit for AMI but K-SADS-derived data did not)
  - Keller et al., 2001 (AMI)
- Total of >500 children and adolescents included in these trials

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Efficacy: Depression

• Positive DBPC trials of TCAs in youth:

Efficacy: SAD/School Phobia

• Positive RCTs of TCAs vs. placebo in youth:
  – Gittelman-Klein & Klein, 1973 (IMI)
  – Bernstein et al., 2000 (IMI)

• Negative RCTs of TCAs vs. placebo in youth:
  – Berney et al., 1981 (CMI)
  – Klein et al., 1992 (IMI)
  – Bernstein et al., 1990 (IMI)

Efficacy: Enuresis

• Dozens of RCTs have found various TCAs to be superior to placebo in treating nocturnal enuresis

• IMI has been the most frequently studied and shows consistently positive results

Efficacy: Enuresis (cont.)

• Rapoport et al. (1978, 1980) found a significant correlation between plasma IMI levels and response to medication in certain subjects, with a subset of “nonresponders” who showed no response even at relatively high plasma levels

• It is thought that lower doses are often effective because the primary mechanism of action involves direct effects in the CNS, not the peripheral anticholinergic effect on the bladder

Adverse Effects

• Anti-muscarinic: dry mouth, constipation, blurred vision
• Anti-histaminergic: sedation, weight gain
• Anti-α1-adrenergic: tachycardia, orthostatic hypotension, dizziness
• ECG changes: prolonged PR, QRS, and QTc; AV block; T-wave flattening; depressed ST segments
• Seizures (0.3% in adults)

Severe Risks

• Sudden death in the context of therapeutic use:
  – Varley et al., 2001:
    • 6 sudden deaths in children taking desipramine
    • 2 sudden deaths in children taking imipramine (1 of the 2 was also taking thoridizane)
  – Causation not established, but cannot be ruled out
Severe Risks (cont.)

- Overdoses are highly lethal, and DMI appears to pose the greatest risk:
  - Amitai & Frischer, 2006:
    - Analyzed mentions of pediatric TCA ingestions recorded from 1983 to 2002 in the American Association of Poison Control Centers Toxic Exposure Surveillance System
    - 168 fatalities in children and adolescents
    - The case fatality rate for DMI was 4- to 12-times greater than for other TCAs (statistically significant)
  - Assess carefully for suicidality
  - Medication must be kept in a safe place to avoid accidental or intentional overdose

Contraindications

- Cardiac conduction abnormalities:
  - Ask about personal and family cardiac history
- Concurrent MAOI
- Seizure disorder
- Suicidality

Drug Interactions

- MAOIs (hypertensive crisis, serotonin syndrome)
- CYP 450 interactions, especially with 2D6 inhibitors
- Levels may be ↑ by MPH, amphetamines, antipsychotics, OCP, thyroid hormone, salicylates, and steroids
- Levels may be ↓ by carbamazepine, phenytoin, phenobarbital, rifampin, alcohol (chronic use), and heavy cigarette smoking
- May ↑ the effects of warfarin

Drug Interactions (cont.)

- Quinidine
  - ↑ TCA levels through 2D6 inhibition
  - additive effects on cardiac conduction
- Anticholinergic effects worsened by other anticholinergic drugs
- Hypotension worsened by α-methylidopa, β-blockers, clonidine, diuretics, and low potency antipsychotics
- Sedation worsened by alcohol, antihistamines, antipsychotics, barbiturates, and other sedatives

Monitoring

- Response and adverse effects (preferably using child/parent and teacher rating scales)
- HR and BP
- Serum drug levels
  - Wait until TCA has reached steady state (takes about 5 days in most children after starting medication or dose ↑)
  - Obtain trough level (12 hours after the last dose)
- ECG at baseline, with dose ↑ (at steady state), and periodically during maintenance

ECG and V.S. Guidelines When Using TCAs in Youth (Daly & Wilens, 1998)

<table>
<thead>
<tr>
<th>Vital Signs</th>
<th>Children</th>
<th>Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>≤110-130*</td>
<td>≤110-120*</td>
</tr>
<tr>
<td>BP</td>
<td>&lt;120/80</td>
<td>&lt;140/90</td>
</tr>
<tr>
<td>ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>&lt;200 msec</td>
<td>&lt;200 msec</td>
</tr>
<tr>
<td>QRS</td>
<td>≤120 msec, &lt;30% over baseline</td>
<td>≤120 msec, &lt;30% over baseline</td>
</tr>
<tr>
<td>QTc</td>
<td>≤460-480 msec</td>
<td>≤460-480 msec</td>
</tr>
</tbody>
</table>

*for 2 consecutive weeks
Choosing a TCA: General Comments

- For OCD, CMI is the TCA of choice
- For ADHD, IMI and DMI are the best studied, but NT, AMI, and CMI have also been found to be effective
- Secondary amines are generally associated with fewer side effects than tertiary amines
- However, DMI (and to a lesser extent, IMI) has been associated with sudden death

Suggested Order of Preference

- OCD: CMI
- ADHD: NT, then IMI, then DMI
- Depression: ??? Probably would start with NT, then IMI or CMI
- Anxiety disorders: IMI, then NT or CMI
- Enuresis: IMI, then NT or CMI

General Dosing Principles

- Need to be cautious: start low, go slow, check serum levels, monitor for toxicity
- High interindividual variability: little relationship between serum levels and daily dose or response (NT may be an exception)
- May need to wait several weeks to months for full response

General Dosing Principles (cont.)

- Optimal doses are usually lowest for treatment of enuresis, somewhat higher for treatment of ADHD, and higher still for treatment of OCD and (?) depression
- TCAs are often dosed BID in children (as opposed to QD in adolescents and adults) because children tend to metabolize them faster and may be more sensitive to side effects
- Taper gradually (e.g., over 10-14 days) to ↓ the risk of a flu-like withdrawal syndrome

Dosing Specifics

- Nortriptyline:
  - Start with 10 mg/day
  - ↑ by 10 mg q4-6 days to 1-2.5 mg/kg/day (max 100 mg/day)
- Imipramine and Desipramine:
  - Start with 25 mg/day or 0.5 mg/kg/day
  - ↑ by similar increments q4-6 days to 1-5 mg/kg/day (max 150 mg/day)
- Clomipramine:
  - Start with 25 mg/day
  - ↑ by 25 mg q4-6days to 1-3 mg/kg/day (max 150 mg/day)
## Health Canada: General Indications

### Benzodiazepines: Labeled Indications (e-CPS, March 2006)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Anx Disorders</th>
<th>Panic Disorder</th>
<th>Insomnia</th>
<th>Periop Med</th>
<th>Sz Disorders *</th>
<th>Skel Musc Spast</th>
<th>Alcohol Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Bromazepam</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Clordiazepoxide</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Clobazam</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Midazolam</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
</tr>
<tr>
<td>Temazepam</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Triazolam</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Yes</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

\* Refer to individual product monographs for more detailed information.

**b. Used in adults and children.**

**N.B.** According to the CPS, lorazepam and nitrazepam are not recommended for use in individuals under 18 years of age. For clobazam, clonazepam, clorazepate, and diazepam, recommendations regarding use in pediatric populations are not available.
# Benzodiazepines: Pharmacokinetic Properties

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approximate Equivalent Oral Dose (mg)</th>
<th>Time to Peak Concentration (hours)</th>
<th>Onset of Actionb</th>
<th>Active Metabolites</th>
<th>Pathway of Metabolism</th>
<th>Approximate Half-life (hours, parent compound and active metabolite)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Long-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>10</td>
<td>0.5 to 4</td>
<td>I</td>
<td>Yes</td>
<td>Oxidation (CYP1A2)</td>
<td>100</td>
</tr>
<tr>
<td>Clorazepate</td>
<td>7.5</td>
<td>0.5 to 2</td>
<td>F</td>
<td>Yes</td>
<td>Oxidation</td>
<td>100</td>
</tr>
<tr>
<td>Diazepam</td>
<td>5</td>
<td>0.5 to 2</td>
<td>F</td>
<td>Yes</td>
<td>Oxidation (CYP1A2, 2C9, 2C19, 3A4)</td>
<td>100</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>15</td>
<td>0.5 to 1</td>
<td>F</td>
<td>Yes</td>
<td>Oxidation</td>
<td>100</td>
</tr>
<tr>
<td><strong>Intermediate-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0.5</td>
<td>1 to 2</td>
<td>I</td>
<td>Yes</td>
<td>Oxidation (CYP3A4)</td>
<td>12 to 15</td>
</tr>
<tr>
<td>Bromazepam</td>
<td>3</td>
<td>1 to 4</td>
<td>I</td>
<td>Yes</td>
<td>Conjugation</td>
<td>8 to 30</td>
</tr>
<tr>
<td>Clobazam</td>
<td>10</td>
<td>1 to 4</td>
<td>I</td>
<td>Yes</td>
<td>Oxidation</td>
<td>10 to 46</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>0.25</td>
<td>1 to 2</td>
<td>I</td>
<td>No</td>
<td>Oxidation (CYP3A4); reduction</td>
<td>20 to 80</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1</td>
<td>2 to 4</td>
<td>I</td>
<td>No</td>
<td>Conjugation</td>
<td>10 to 20</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>5</td>
<td>2 to 3</td>
<td>I</td>
<td>No</td>
<td>Reduction</td>
<td>16 to 55</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>15</td>
<td>2 to 4</td>
<td>S</td>
<td>No</td>
<td>Conjugation</td>
<td>5 to 15</td>
</tr>
<tr>
<td>Temazepam</td>
<td>15</td>
<td>2 to 3</td>
<td>I</td>
<td>No</td>
<td>Conjugation</td>
<td>10 to 20</td>
</tr>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolamc</td>
<td>Not applicable</td>
<td>See Onset of Action</td>
<td>I.M.: 5 to 15 min I.V.: 1.5 to 5 min</td>
<td>Yes</td>
<td>Oxidation (CYP3A4)</td>
<td>1 to 4</td>
</tr>
<tr>
<td>Triazolam</td>
<td>0.25</td>
<td>1 to 2</td>
<td>F</td>
<td>No</td>
<td>Oxidation (CYP3A4)</td>
<td>1.5 to 5</td>
</tr>
</tbody>
</table>

---

**a.** After oral administration.

**b.** Legend: F = fast (< 1 h); I = intermediate (1–3 h); S = slow (> 3 h).

**c.** Parenteral use only.

**d.** Onset of action may be faster if opioid administered concurrently.
Minimum Age of FDA Approval and Typical Pediatric Doses

TABLE 1
Benzodiazepines Categorized by Half Life and Potency

<table>
<thead>
<tr>
<th>Generic name (trade name)</th>
<th>Onset of action</th>
<th>Elimination half-life (hrs)</th>
<th>Metabolism</th>
<th>Minimum age approved</th>
<th>Typical cited daily dosage (Reference#)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Long half-life (&gt;13 hrs) high potency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonazepam (Klonopin)</td>
<td>Intermediate</td>
<td>18–50</td>
<td>Oxidation nitroreduction</td>
<td>Not specified</td>
<td>0.5–3.0 mg/day (14,15)</td>
</tr>
<tr>
<td>II. Long half-life (&gt;13 hrs) low potency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlordiazepoxide (Librium)</td>
<td>Intermediate</td>
<td>5–100</td>
<td>Oxidation</td>
<td>6 years</td>
<td>5 mg bid-qid, Max dose: 30 mg/day (16)</td>
</tr>
<tr>
<td>Diazepam (Valium)</td>
<td>Fast</td>
<td>30–100</td>
<td>Oxidation</td>
<td>6 months</td>
<td>0.1–0.3 mg/kg/day max dose: 1-2.5 mg tid-qid (17)</td>
</tr>
<tr>
<td>Flurazepam (Dalmane)</td>
<td>Fast</td>
<td>50–100</td>
<td>Oxidation</td>
<td>15 years</td>
<td>15–30 mg at bedtime (17)</td>
</tr>
<tr>
<td>Chlorazapate (Tranxene)</td>
<td>Fast</td>
<td>30–100</td>
<td>Oxidation</td>
<td>9 years</td>
<td>7.5 mg bid, Max dose: 60 mg/day (17)</td>
</tr>
<tr>
<td>III. Short half-life (&lt;13 hrs) high potency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorazepam (Ativan)</td>
<td>Intermediate</td>
<td>10–20</td>
<td>Conjugation</td>
<td>12 years</td>
<td>1–6 mg/day (17)</td>
</tr>
<tr>
<td>Alprazolam (Xanax)</td>
<td>Intermediate</td>
<td>6–20</td>
<td>Oxidation</td>
<td>18 years</td>
<td>0.5–6.0 mg/day (18–22)</td>
</tr>
<tr>
<td>Triazolam (Halcion)</td>
<td>Fast</td>
<td>1.7–3.0</td>
<td>Conjugation</td>
<td>18 years</td>
<td>0.125–0.25 mg at bedtime (17)</td>
</tr>
<tr>
<td>IV. Short half-life (&lt;13 hrs) low potency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxazepam (Serax)</td>
<td>Slow</td>
<td>5–21</td>
<td>Conjugation</td>
<td>6 years</td>
<td>10 mg tid for adolescents (17)</td>
</tr>
<tr>
<td>Temazepam (Restoril)</td>
<td>Slow</td>
<td>10–12</td>
<td>Conjugation</td>
<td>18 years</td>
<td>15–30 mg at bedtime (17)</td>
</tr>
</tbody>
</table>
### Table 1. Relative Restrictions of Foods and Beverages With MAOI Use

<table>
<thead>
<tr>
<th>Restriction</th>
<th>Foods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute</td>
<td>Aged cheeses; aged and cured meats; banana peel; broad bean pods; improperly stored or spoiled meats, poultry, and fish; Marmite; sauerkraut; soy sauce and other soybean condiments; and tap beer</td>
</tr>
<tr>
<td>Moderate</td>
<td>Red or white wine, bottled or canned beer (including nonalcoholic varieties)</td>
</tr>
<tr>
<td>Unnecessary</td>
<td>Avocados; bananas; beef/chicken bouillon; chocolate; fresh and mild cheeses, e.g., ricotta, cottage, cream cheese, processed slices; fresh meat, poultry, or fish; gravy (fresh); monosodium glutamate; peanuts; properly stored pickled or smoked fish, e.g., herring; raspberries; soy milk; yeast extracts (except Marmite)</td>
</tr>
</tbody>
</table>

### Table 2. Sunnybrook Health Science Centre MAOI Diet

Several foods and beverages contain tyramine and may interact with your medication. You MUST follow the dietary instructions below from the day you start taking the medication until 2 weeks after stopping it.

**Note:** All foods must be fresh or properly frozen. Avoid foods when you are unaware of storage conditions.

<table>
<thead>
<tr>
<th>Food to Avoid</th>
<th>Food Allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheese</td>
<td></td>
</tr>
<tr>
<td>All matured or aged cheese</td>
<td>Fresh cottage cheese, cream cheese, ricotta cheese, and processed cheese slices. All fresh milk products that have been stored properly (e.g., sour cream, yogurt, ice cream)</td>
</tr>
<tr>
<td>All casseroles made with these cheeses, i.e., pizza, lasagna, etc.</td>
<td></td>
</tr>
<tr>
<td>Please note: All cheeses are considered matured or aged except those listed opposite</td>
<td></td>
</tr>
<tr>
<td>Meat, fish, and poultry</td>
<td></td>
</tr>
<tr>
<td>Fermented/dry sausage; pepperoni, salami, mortadella, summer sausage, etc. Improperly stored meat, fish, or poultry</td>
<td>All fresh packaged or processed meat (e.g., chicken loaf, hot dogs), fish, or poultry. Store in refrigerator immediately and eat as soon as possible</td>
</tr>
<tr>
<td>Fruits and vegetables</td>
<td></td>
</tr>
<tr>
<td>Fava or broad bean pods (not beans) Banana peel</td>
<td>Banana pulp All others except those listed opposite</td>
</tr>
<tr>
<td>Alcoholic beverages</td>
<td></td>
</tr>
<tr>
<td>All tap beers</td>
<td>Alcohol: No more than two domestic bottled or canned beers or 4-fl-oz glasses of red or white wine per day; this applies to nonalcoholic beer also; please note that red wine may produce headache unrelated to a rise in blood pressure</td>
</tr>
<tr>
<td>Miscellaneous foods</td>
<td></td>
</tr>
<tr>
<td>Marmite concentrated yeast extract Sauerkraut Soy sauce and other soybean condiments</td>
<td>Other yeast extracts (e.g., brewer’s yeast) Soy milk</td>
</tr>
</tbody>
</table>

Reference: Gardner et al., 1996
## Drug Interactions: AED’s

**Table 3: Summary of AED Interactions with TOPAMAX®**

<table>
<thead>
<tr>
<th>AED Co-administered</th>
<th>AED Concentration</th>
<th>Topiramate Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>NC or 25% increase (^a)</td>
<td>48% decrease</td>
</tr>
<tr>
<td>Carbamazepine (CBZ)</td>
<td>NC</td>
<td>40% decrease</td>
</tr>
<tr>
<td>CBZ epoxide (^b)</td>
<td>NC</td>
<td>NE</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>11% decrease</td>
<td>14% decrease</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>NC</td>
<td>NE</td>
</tr>
<tr>
<td>Primidone</td>
<td>NC</td>
<td>NE</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>NC at TPM doses up to 400 mg/day</td>
<td>15% increase</td>
</tr>
</tbody>
</table>

\(^a\) = Plasma concentration increased 25% in some patients, generally those on a b.i.d. dosing regimen of phenytoin.

\(^b\) = is not administered but is an active metabolite of carbamazepine.

NC = Less than 10% change in plasma concentration.

AED = Antiepileptic drug.

NE = Not Evaluated.

TPM = Topiramate

Reference: www.pdr.net

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