

**Pharmacologic Management
of
Anxiety and Depression**

Donald B. Milligan, M.D.
Clinical Assistant Professor
Department of Family Practice
University of Kansas Medical Center

Prescripto Ergo Sum

Most health care workers are
interventionists

- Urge to “make someone better” sometimes overrides reality
- “Don’t just do something, stand there!”

Dwight Eisenhower

Hazardous Patient Beliefs

- There is always a cure! :(NOT!)
- My current discomfort requires medication.
- Discomfort with my current situation is a medical problem.
- A “good doctor (or nurse)” will give me a medicine.
- I shouldn’t have to go through an exam, since I already know what I have.

**Primum non nocere
(Kill as few patients as possible)**

- All prescriptions have side effects.
- Prescription is always easier than educating--until the next visit.
- Adverse drug reactions 4th to 6th greatest cause of death in adults
- Just because you mean well and please the patient doesn't mean he'll be your friend in court.

Insomnia

- One of the most common problems in medicine:
 - in a given year 25-35% of patients will experience insomnia; 17% as a serious problem.
- 2 to 4 % of these patients use hypnotics in one form or another in a given year.

Insomnia

- Vast majority of insomniacs who use drugs use OTC drugs (3-4% of population)
- Most drug use short-term or intermittent for one day to as much as 2 weeks.
- Most insomniacs (85%) do not use drugs at all, although they may rate the problem as serious.

**Type of Sleep Disturbance
Important in Prescribing**

- sleep onset disorder
- nocturnal awakenings
- early a.m. wakenings

**International Classification
of Sleep Disorders**

1. Dyssomnias
 - A. Intrinsic sleep disorders
 - B. Extrinsic sleep disorders
 - C. Circadian rhythm sleep disorders

**International Classification
of Sleep Disorders**

2. Parasomnias
 - A. Arousal disorders
 - B. Sleep-wake transition disorders
 - C. Parasomnias usually associated with REM sleep
 - D. Other Parasomnias

International Classification of Sleep Disorders

3. Medical/Psychiatric sleep disorders
 - A. Associated with mental disorders
 - B. Associated with neurologic disorders
 - C. Associated with other medical disorders

Treatment of Insomnia

Nonpharmacologic treatment best where possible:

- Set regular time for sleep
- Comfortable and secure environment
- Omit EtOH and caffeine late in day (depending on sensitivity)
- Bedroom only for sleep (or sex)
- Watch for effects of meals and exercise
- Relaxation techniques, meditation, or hypnosis
- Consider psychotherapy

Drugs for Sleep

OTC commonly used:

diphenhydramine (Benadryl or Sominex 2) 25-50 mg.
doxilamine (Unisom)

L-tryptophan popular for a while, but; efficacy unclear, unpredictable.

Eosinophilia-myalgia syndrome has suspended sale for sleep in US.

Melatonin currently promising (&popular), but only a few studies as yet (time zone readjustment)

CME lectures useful in specific populations--may require conditioning for full efficacy.

Drugs for Sleep

Barbiturates

- Pentobarbital (Nembutal)
- Secobarbital (Seconal)
- Amobarbital (Amital)

Once most widely used, but:

- Narrow margin of safety
- Moderately high potential for abuse
- Drug interactions
- Suppression of delta and REM sleep
- REM rebound on withdrawal

Drugs for Sleep

Nonbarbiturate, nonbenzodiazepines

methaqualone (Quaalude): high abuse potential

Glutethimide: CNS depressant plus anticholinergic

Chloral hydrate: not too many problems, but displaces protein-bound drugs, cross reacts with EtOH

Drugs for Sleep

Benzodiazepines: probably the drugs of choice if drug therapy is chosen currently.

- Not problem-free, but safer than most other drugs.
- Watch for onset, duration of action of not only parent drug, but of any active metabolites.
- Basically any benzodiazepine *may* be used, but only a few commonly used for sleep.

Benzodiazepines for Sleep

- Flurazepam (Dalmane): dose 15-30 mg. , long-lasting metabolite occasionally a problem, especially in elderly.
- Triazolam (Halcion): short-acting (avg. 4-6 hours) antegrade amnesia occasionally a problem.
- Temazepam (Restoril): short-acting (avg. 6-8 hours) may still accumulate in elderly.
- Quazepam (Doral): selective for BZ1 receptor (?), BUT same long-acting metabolite as flurazepam
- Estazolam (ProSom): apparently a "faster-acting temazepam."

Benzodiazepines for sleep

Notice absence of diazepam, chlorazepate, chlordiazepoxide, from list of sleep drugs--either too long acting or metabolites are.

Benzodiazepines for Sleep

- Drug withdrawal insomnia
- Rebound insomnia
- REM rebound
- Withdrawal siezures can occur

All apparently treatable by gradual tapering of dose or replacement by a long-acting drug with taper.

Nonbenzodiazepine Sleep Agent: Zolpidem (Ambien)

- nonbenzodiazepine, but many similar properties. Not apparently as prone to tolerance with long-term use.
- apparently does not change sleep stages
- no apparent tolerance
- 6-8 hour action (like temazepam)

New Nonbenzodiazepine Sleep Agent: Zaleplon (Sonata)

Affects omega (BZ)1 receptors.
Duration of action approx. 4 hours
(serum $T_{1/2}$ - 1 hr)
Very little hangover in most studies.

Zaleplon & Zolpidem

- Neither drug has significant anticonvulsant or muscle relaxant qualities.
- Little evidence for withdrawal.
- Costly (\$2.21 and \$2.17 respectively per tablet)

Drug Therapy of Insomnia

Do not use in:

- sleep apnea
- substance abuse
- pregnancy
- suicidal patients may actually succeed with BZ's if combined with large doses of EtOH

Therapy of Anxiety

- Anxiety tends to exist in the same environment as insomnia, but not necessarily in same patients.
- Drug therapy similar, but not identical

Classification of Anxiety

- Generalized anxiety disorder
- Panic disorder
 - with agoraphobia (more common in women)
 - without agoraphobia (no sex difference)
- Agoraphobia without panic disorder
- Social Phobias
- Simple phobias
- Obsessive-compulsive disorder
- Post-traumatic stress disorder

Treatment of Anxiety

Nonpharmacologic treatment

- supportive therapy
- education about anxiety and the autonomic nervous system
- exposure therapy
- cognitive therapy
- relaxation techniques

Nonpharmacologic treatment may be insufficient alone, but combination with drug therapy may be more effective than either method alone.

Generalized Anxiety Disorder

Chronic difficult to control anxiety with:

1. restlessness or feeling "on edge"
2. easily fatigued
3. difficulty concentrating
4. irritability
5. Muscle tension
6. sleep disturbance

Therapy of Anxiety

Generalized Anxiety Disorder

- Psychotherapy preferred as part of treatment
- Medications:
 - Benzodiazepines
 - Guidelines of "short-term, limited dose" difficult
 - Addictive potential of benzodiazepines (?)
 - Buspirone
 - Beta adrenergic blockers
 - Barbiturates and meprobamate
 - Antihistamines
 - hydroxyzine, diphenhydramine, etc.

Therapy of Anxiety

Drug therapy (continued)

- MAO inhibitors
- Tricyclic antidepressants (clomipramine often selectively used for OCD--though not allowed in graduate school)
- Selective serotonin reuptake inhibitors

Benzodiazepines

- Alprazolam (Xanax): most potent and, some argue, most addictive
- Chlordiazepoxide (Librium): oldest, still effective, metabolite active
- Clonazepam (Klonopin): often used for restless leg syndrome and occasionally for seizure disorders
- Clorazepate (Tranxene): Longest-acting, often useful in long-term therapy, somewhat less reinforcing effects

Benzodiazepines Cont.

- Diazepam (Valium): probably best known, some patient resistance due to publicity though not so bad now, active metabolite with 150-200 hr half-life.
- Lorazepam (Ativan): good IM, no significant active metabolites
- Oxazepam (Serax) rarely used, still available generically.

Benzodiazepines

Adverse drug reactions do occur:

- sedation, psychomotor impairment, ataxia
- anterograde amnesia: watch for forgetfulness
- paradoxical excitement
- aggression
- confusion, disorientation
- aggravation of depression

Drug-drug interactions not rare

Addictive problems

- dependence, withdrawal, tolerance, abuse

Benzodiazepine Toxicity

- Be aware that, contrary to popular belief, it is apparently possible to kill yourself with benzodiazepines if mixed with sufficient alcohol.
- Above especially relevant in view of exacerbation of depression.

Buspirone

Mechanism of action unclear

Efficacy equal to that of BZ's in controlled studies, but:

- slower onset
- no significant anticonvulsant, muscle relaxant or hypnotic properties
- disliked by benzodiazepine "fans"

Buspirone

Side effects:

- dizziness (15-20%)
- nausea
- headache
- nervousness (especially in previous BZ users)
- light-headedness

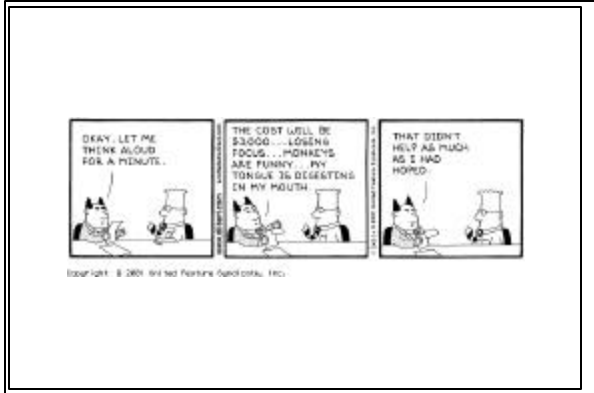
Lack of addictive potential may make patients (and prescribers) more willing.

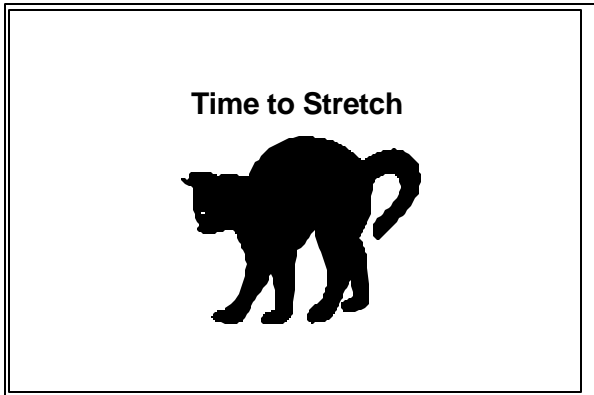
Beta Adrenergic Blockers

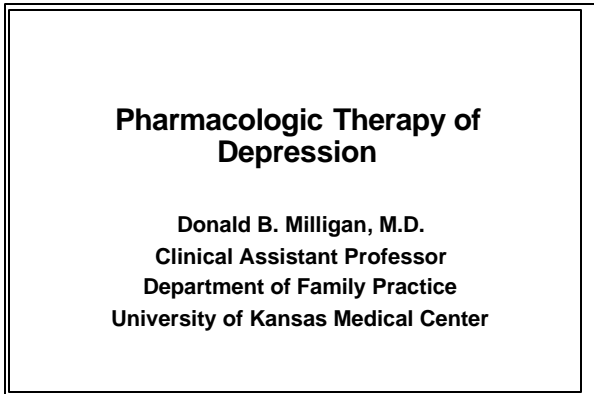
- Not specifically indicated for anxiety.
- Useful for blocking physiologic symptoms of specific stressful situations.
- May be useful in PTSD.
- Useful for performance anxiety (concerts)

Antidepressant Drugs

- Best-tested in panic disorders, OCD
- TCA's and SSRI's seem equally effective
- Cost: TCA's cheaper, SSRI's "cleaner"
- MAOI's useful in phobias







Mood Disorders

- Widespread in population: lifetime incidence approximately 10%
- Strong genetic substrate: 65% of bipolar disorder patients have a first degree relative with the disorder.
- 6-month prevalence: 4% for women, 2% for men
- Lifetime prevalence of depression: 5-9% for women, 2-4% for men
- Major depression: 40% recover with no recurrence, 20% chronic

Classification of Mood Disorders

- Bipolar disorder
 - Manic
 - Depressed
- Major Depression
 - Single episode
 - Recurrent
- Cyclothymia
- Dysthymia
- Seasonal affective disorder
- "Unofficial subtypes" of depression
 - Double depression
 - Psychotic depression
 - Atypical depression

Clinical Features of Depression

Physiologic:

- Sleep disturbance, typically decreased
- Change in appetite and weight, typically decreased--change >5% (DSM-IV)
- Loss of energy, fatigue
- Psychomotor agitation or retardation
- Decreased libido
- Menstrual irregularities
- Palpitations, constipation, headache
- Other nonspecific bodily complaints

Clinical Features of Depression

Psychologic

- Dysphoric mood (sad, despondent, discouraged)
- Excessive guilt
- Pessimism, hopelessness, self-pity
- Loss of interest in usual activities (anhedonia)
- Social withdrawal

Clinical Features of Depression

Thinking:

- Decreased concentration and attention span
- Confusion, poor memory
- Slowed thought processes
- Persecutory, somatic, or religious delusions
- Suicidal ideation

Dysthymia: Depression for Clinicians!

- Dysthymic patients are the most common recipients of inappropriate antidepressant medications.
- Characterized by chronic mild depression without sufficient symptoms to meet criteria for Major Depressive Episode.
- Problem with "Double depression:" major depressive symptoms resolve, but chronic depressive behavior continues.

Treatment of Depression

- Psychotherapy
- ECT
- MAOI's
- TCA's
- SSRI's
- Buspirone
- Lithium

Treatment of Depression

Psychotherapy

- Once weekly psychotherapy equally effective with TCA's or SSRI's in ambulatory patients.
- Combination therapy with drugs more effective than either therapy alone.
- Improves: psychosocial function
interpersonal relationships
day-to-day coping

Electroconvulsive Therapy (ECT)

- Remains the most effective treatment for major depression
- More effective, more rapid onset, safer for patients with heart disease than TCA's
- Disadvantages:
 - frequent relapse following termination of therapy
 - temporary memory loss
 - social stigma
 - legal barriers

Drug Therapy of Depression

Stimulants:

- Little clear support
- Best evidence for efficacy is brief, low-dose therapy in apathetic "senile" institutionalized geriatric patients with expectation of only partial improvement
- Methylphenidate 20-30mg/day for 2-4 weeks is usually tolerated better than TCA's in this population, with the only major side effect being exacerbation of pre-existing anxiety

Monoamine Oxidase Inhibitors

Effective for Specific Patients:

- Atypical depression
- Panic disorder
- Some phobic disorders
- Treatment failures with TCA's or SSRI's
- Severe reactions from food are well-known, but fortunately, are rarely seen.
- Hypertensive reactions more common from drugs: sympathomimetics, stimulants, L-DOPA, meperidine

Drugs for Treatment of Depression

Tricyclics:

- amitriptyline (Elavil)
- imipramine (Tofranil)
- desipramine (Norpramin, Pertofrane)
- nortriptyline (Pamelor)
- trimipramine (Surmontil)
- protriptyline (Vivactil)
- doxepin (Sinequan, Adapin)

Tetracyclics:

- maprotiline (Ludiomil)

Drugs for Treatment of Depression

- Dibenzoxazepine
amoxapine (Asendin)
- Triazolopyridine
trazodone (Desyrel)
nefazodone (Serzone)
- Buspirone (Buspar)
high dose: 40-80 mg
- Bicyclic
fluoxetine (Prozac)
sertraline (Zoloft)
paroxetine (Paxil)
fluvoxamine (Luvox)
citalopram (Celexa)
- Monocyclic animoketone
bupropion (Wellbutrin)

Drugs for Treatment of Depression

- Venlafaxine (Effexor)-a phenylethylamine which inhibits reuptake of serotonin, norepinephrine and dopamine (somewhat)
- Mirtazapine (Remeron) noradrenergic and specific serotonergic agent with a high affinity for both receptors
- Citalopram (Celexa) functionally, an SSRI, but structurally dissimilar

Drug Therapy of Depression

So what's the "drug of choice?"
No single answer

- Look for:
 - previous response
 - side effect profile
 - adverse
 - positive
 - patient attitude (predictive of compliance)
- Watch out in the elderly!
- Drug plasma levels variably useful (TCA's).

Treatment-Resistant Depression

- Approximately 30% of patients do not respond to a trial of antidepressant therapy.
- Reassess diagnosis (remember dysthymia?)
- Lithium?
- Check for adequacy of drug dosages
most common problem is underdosage of drugs, especially TCA's
- Check thyroid profile

Bipolar Disorder

- Lithium the drug of choice for acute manic episodes but requires 7-10 days for effect.
- Concomitant use of antipsychotics often needed
- Lithium alone or in combination with antidepressants is a useful long term therapy, but not required by every patient.
- Valproic acid, SSRI's also used, though not considered drugs of choice

Comparison of Newer Antidepressants

- Nausea: Prozac 21%
 - Zoloft 26%
 - Paxil 26%
 - Effexor 37%
 - Serzone 22%
 - Celexa 21%

Comparison of Newer Antidepressants

- **Insomnia:** Prozac 14%
 Zoloft 16%
 Paxil 13%
 Celexa 13%

Comparison of Newer Antidepressants

- **Drowsiness:** Prozac 12%
 Zoloft 13%
 Paxil 23%
 Remeron 54%
 Effexor 23%
 Celexa 13%

Comparison of Newer Antidepressants

- **Dizziness:** Prozac <5%
 Zoloft 12%
 Paxil 13%
 Effexor 19%
 Serzone 10%("Lightheaded")
 Celexa 2%

“Unique” Side Effects of Antidepressants

- Remeron and Ludiomil: Wt. Gain 12%
- Wellbutrin: agitation 32%, also decreases craving for tobacco (?cocaine)
- Effexor: abnormal ejaculation 12%
male impotence 6%

Drug Therapy of Depression

General guidelines:

- Be careful in diagnosis
- After selecting a drug, make sure doses are adequate
- Look for intercurrent illness
- Beware of triggering mania (check for family history of bipolar disorder)
- Probably safest drugs (though expensive) are SSRIs, buspirone, newer mixed agents
- Remember psychotherapy
- Consider ECT referral
