TRICYCLIC ANTIDEPRESSANTS: A CLINICAL UPDATE

I. The DSM-III and Depression

A. Major Syndromes

1. Major depressive disorder
2. Dysthymic disorder
3. Atypical depressive disorder

B. Major Dichotomies

1. Primary vs. Secondary
2. Unipolar vs. Bipolar
3. Single vs. Recurrent
4. Psychotic vs. Non-psychotic
5. Melancholic (endogenous) vs. Non-melancholic

II. Tricyclic Antidepressants

A. Efficacy

1. No treatment $\simeq$ 25%
2. Placebo $\simeq$ 40%
3. Drug $\simeq$ 70%

B. Current Agents

Drug	Example	Ave. dose mg.	Comment/Claims
1. Tetracyclic			
Maprotiline	Ludiomil	150-300	Fewer side effects?
2. Tricyclics-Tertiary Amines			
Imipramine	Tofranil	150-300	First one
Amitriptyline	Elavil	150-300	Most sedating & anticholinergic

Drug	Example	Ave. dose mg.	Comments/Claims
Doxepin	Sinequan	75-300	Sedating; less cardiotoxic ?
Amoxapine	Asendin	200-400	Rapid onset? dibenzoxazepine
Chlorimipramine	Anafranil	150-300	Obsessive-compulsive disorders?
Trimipramine	Surmontil	75-200	Mild-moderate depression; sleep
3. Tricyclics-Secondary Amines			
Desipramine	Norpramin	100-300	Mild sedation & anticholinergic activity
Nortriptyline	Aventyl	50-150	Therapeutic window
Protriptyline	Vivactil	10-60	Least sedating

C. Reported Uses

1. "Biological" depressions
2. "Reactive" depressions
3. Alcoholism
4. Chronic pain
5. Narcotic withdrawal
6. Hyperkinesis

7. Enuresis
8. Obsessive-compulsive disorder
9. Schizoaffective disorders

D. Mechanism of Action
   1. ?Block of pre-synaptic reuptake of monoamine neurotransmitters
   2. ?Anticholinergic activity

E. Specificity
   1. Behavioral criteria
      a) Agitation (amitriptyline) vs. retardation (imipramine)?
      b) Psychoses
   2. Side effects
      a) Sedation
      b) Anticholinergic
      c) Cardiovascular (decreased blood pressure and conduction)
   3. Age
   4. Previous response
   5. Genetic similarity
   6. Biological - see section II F-2 below

F. Predictors of Response
   1. Psychosocial-clinical Predictors
      a) Good response (large drug-placebo difference)
         1) upper socioeconomic class

2) insidious onset

3) anorexia and weight loss

4) middle, late insomnia

5) psychomotor retardation or agitation

b) Poor response (small drug-placebo difference)

1) neurotic, hypochondriacal, hysterial traits

2) multiple prior episodes

3) delusions?

2. Biological Predictors

a) Biogenic amine metabolites- 3-methoxy 4-hydroxy-phenylglycol (MHPG) and 5-hydroxyindolacetic acid levels (5HIAA)

Drug	Effect on Reuptake		
	5'HT	NE	DA
Chlorimipramine	5	0	0
Desmethylchlorimipramine	1	2	0
Amitriptyline	4	0-1	0
Nortriptyline	2	3	0
Imipramine	3	2	0
Desipramine	0	4	0
Maprotiline	0	5	0
Amphetamine		3	4

1) Type A patients
   - low pretreatment urinary MHPG levels
   - normal or high pretreatment CSF 5HIAA levels
   - a favorable response to imipramine or desipramine
   - a brightening of mood following a trial of dextroamphetamine
   - a modest increment or no change in MHPG level following treatment
   - a poor response to amitriptyline
2) Type B patients
   - a normal or high urinary MHPG level
   - low CSF 5HIAA levels
   - failure to respond to imipramine
   - a lack of mood change during a trial of dextroamphetamine
   - a decrement in urinary MHPG following treatment with imipramine, desipramine or dextroamphetamine
   - a favorable treatment response to amitriptyline

b) Catechol-o-methyltransferase (COMT)
   1) low erythrocyte levels - positive response to imipramine
   2) higher levels require higher doses

c) Sleep EEG within 2 days

1) decrease in percentage REM sleep
2) increase in REM latency (i.e., restoration of Stage IV)
3) decrease REM activity

d) Neuroendocrinology of "biological" depressions
1) Cortisol
a) increased in "vital" depression
b) failure of dexamethasone suppression
i. sensitivity - 65%
ii. specificity - 95%
iii. "escapers" may be more severe and better responders
2) growth hormone - reduced growth hormone response to insulin induced hypoglycemia or amphetamine challenge
3) thyroid hormone - subnormal increase in blood TSH after TRF challenge

G. Relative Contraindications/Precautions
1. Glaucoma
2. Prostatic hypertrophe
3. Use with caution in the presence of recent myocardial infarction, heart block, sick sinus syndrome or congestive heart failure.

H. "Common" Side Effects

1. Sedation (especially amitriptyline and doxepin)

2. Anticholinergic

a) Central anticholinergic syndrome

1) Signs

a) florid visual hallucinations

b) loss of immediate memory

c) disorientation

d) agitation

e) hyperthermia

f) pseudoseizures

g) mydriasis

2) Treatment

Physostigmine iv or im (1-2 mg q 30 minutes)

b) Peripheral Effects

1) Signs (essentially anticholinergic)

a) dry mouth

b) constipation

c) paralytic ileus (rare)

d) urinary retention

e) loss of accommodation

f) glaucoma

g) palpitations

h) tachycardia

i) hypotension

2) Treatment

Lozenges - Bethanechol 25 mg tid

3. Adrenergic Stimulation
   a) tremor
   b) jitteriness
   c) changes in cold and heat tolerance
   d) tachycardia
4. Behavioral
   a) precipitating manic episodes
   b) worsening schizophrenic episode
5. Allergic and hypersensitivity effects
   a) jaundice (rare)
   b) agranulocytosis (rare) or leukocytosis
6. Galactorrhea (rare)
7. Cardiovascular
   a) orthostatic hypotension
      1) not dose related
      2) no tolerance
   b) cardiac depressant effects
   c) tachycardia
   d) electrocardiographic effects
      1) therapeutic doses
         a) slow conduction through A-V node (esp. Bundle of His)

b) prolongation of PR, QRS and QT intervals

c) T-wave inversion or flattening

d) ST-segment depression

e) quinidine-like (anti-arrhythmic) effect

f) increase pre-existing changes

g) reports of myocardial infarction, congestive heart failure, and sudden death

2) toxic doses

a) sinus tachycardia

b) QRS-segment increases

c) A-V block

d) bundle branch blocks

e) ventricular premature contractions

f) ventricular tachycardia

g) ventricular fibrillation → bradycardia → arrest → death

3) variables affecting cardiovascular side effects

a) age

b) cardiac status

c) differential effects of specific drugs

I. Blood Levels

1. Wide variability between dose and plasma level

a) Nortriptyline

1) Curvilinear relationship

2) 50-150 ng/ml

b) Imipramine (imipramine and desipramine)

1) linear relationship

2) $\leq$ 180 ng/ml poor

3) 180-240 ng/ml intermediate

4) $>$ 240 mg/ml best

c) Amitriptyline (amitriptyline and nortriptyline)

1) probably linear relationship

2) $>$120 ng/ml

d) Others less conclusive

2. Uses

a) assess non-response

b) assess "extra-sensitive" patients

c) clinical monitoring in high risk patients

1) cardiac patients

2) geriatric patients

J. Withdrawal Effects (usually minimal)

1. Nausea and vomiting

2. Malaise

3. Headache and muscle aches

4. Anxiety and akathisia

K. Drug-Drug Interactions

1. Antihypertensive agents

a) guanethidine, bethanidine, debrisoquine and clonidine

1) blocks amine pump

2) lessens antihypertensive effect

b) reserpine, alpha-methyldopa, propanlol

1) increase depression

2) ?central loss of blood pressure control

3) decrease contractibility

2. Sympathomimetics (norepinephrine, epinephrine, phenylephrine, methylphenidate)

a) potentiation of pressor response

b) hypertensive crisis

3. Sedative-hypnotics (barbiturates, alcohol)

a) potentiation of CNS and respiratory depressant effects

b) stimulation of microsomal enzymes

c) decrease blood levels of tricyclic antidepressants

4. Phenothiazines

a) compete for same hepatic microsomal enzymes

b) anticholinergic and hypotensive effects may be additive or potentiated

c) raise plasma tricyclic antidepressant levels

5. Oral anticoagulants

a) tricyclics may impair hepatic metabolism

b) excessive anticoagulation

6. Anticholinergic drugs

a) potentiation

b) central anticholinergic syndrome

7. Other

a) methylphenidate elevates plasma levels of imipramine and desipramine

b) aspirin and haloperidol increase plasma concentrations of nortriptyline

c) Disulfiram raises plasma levels

d) oral contraceptives reduce nortriptyline levels in patients receiving amitriptyline

e) smoking lowers plasma levels of imipramine

L. Combinations

1. MAO Inhibitors

a) use in "refractory" depressions

b) safety

c) guidelines

1) reasonable doses

2) start simultaneously or tricyclic first

3) no other CNS drugs

4) usual dietary and other precautions

5) amitriptyline vs. imipramine

2. Thyroid medications (Triiodothyronine)

a) accelerate and/or potentiate action

b) men vs. women

3. Methylphenidate

a) increase plasma level

b) accelerate and/or potentiate

4. Biogenic amine precursors

a) L-dopa

b) Tryptophan

c) 5 hydroxytryptophan (5 HTP)

M. Clinical Considerations

1. Need adequate dose for at least 2-3 weeks for fair trial
2. Long half-life; may be given once daily
3. Natural history of untreated depressive episode (unipolar) 6-9 months; may need prolonged treatment
4. Recurrence rate of depression high; may need prolonged treatment
5. Specific drug may be influenced by most or least desirable side effects
6. Older patients "often" require lower doses
7. Overdose may be lethal (LD_{50} is about one week supply)
8. If non-response:

a) consider non-compliance

b) consider drug-drug interaction

c) consider high or low blood level

d) consider other class of tricyclic or other antidepressant treatment

e) consider diagnostic error

III. Monoamine Oxidase Inhibitors

A. Efficacy

1. Endogenous depression

2. Other depressions

B. Current agents

1. Hydrazine

a) Phenelzine (Nardil) 30-90 mg

b) Isocarboxazid (Marplan) 20-80 mg

2. Non-hydrazines

Tranylcypromine (Parnate) 20-60 mg

C. Indications

1. hypertension

2. depression

a) atypical

1) mixed anxiety-depression

2) hysteroid dysphoria

3) reversed vegetative symptoms

4) masked depression

5) mild depression

b) major depressive disorder (endogenous)

3. phobic anxiety syndrome

4. hostile depressions

5. where tricyclics are ineffective

D. Presumed Mechanisms of Action

1. blocks metabolism of monoamines (5HT, NE, DA)

2. causes buildup of monoamines

E. Determining Optimal Dosage

1. ≥80% inhibition of platelet MAOI

2. 60 mg vs. 30 mg Nardil

F. Side Effects

1. Behavioral

a) hyperactivity

b) agitation

c) irritability

d) confusion

e) precipitate manic episode

f) insomnia

g) headaches

2. Autonomic

a) orthostatic hypotension

b) dry mouth

c) blurred vision

d) constipation

e) urinary retention

f) impotence

g) dizziness

3. Hypoglycemia

4. Cardiovascular

a) hypertensive (amphetamine-like)

b) hypotensive (orthostatic)

5. Gastrointestinal
   a) hepatotoxicity
   b) nausea
   c) vomiting
   d) diarrhea
6. Hypertensive crisis
   a) Symptoms
      1) tachycardia
      2) hyperpyrexia
      3) hypertension
      4) prostration
      5) sweating
      6) confusion
      7) agitation
      8) headache--photophobia "meningismus"
      9) CVA's
   b) Causes
      1) sympathomimetics (amphetamines, cold preparations)
      2) tyramine-containing foods (see PDR - Chianti wine, fermented cheeses, chicken liver, pickled herring, broad beans, etc.)
      3) L-dopa
      4) Meperidine or dextromethorphan

5) tricyclic antidepressants

c) Treatment

1) symptomatic

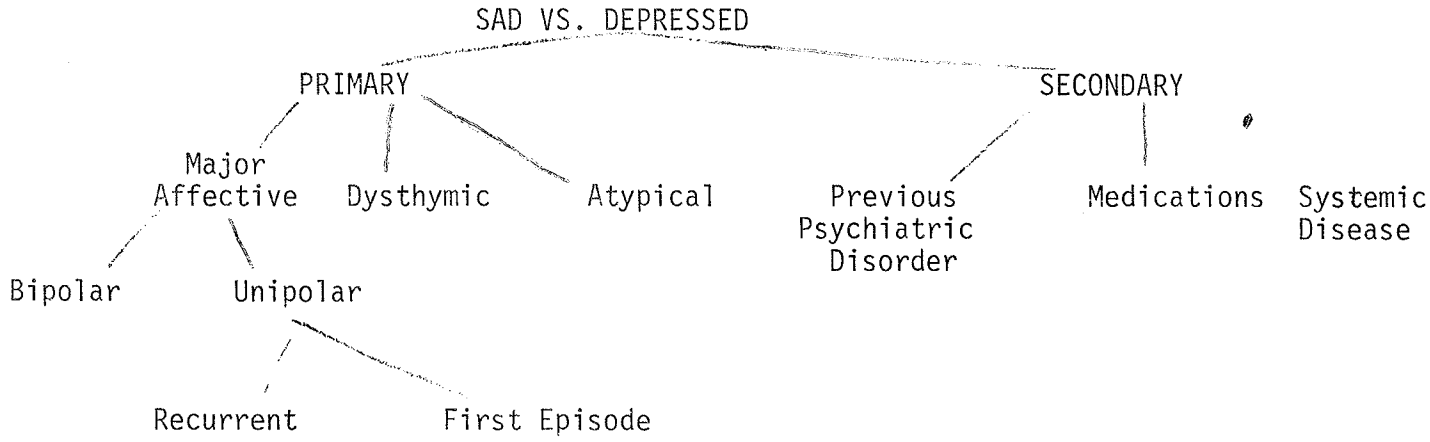
2) chlorpromazine or phentolamine

G. Comments

1. Underutilized in this country

2. To be used only when patients can clearly understand and are likely to adhere to the dietary precautions

IV. A Decision Tree



ANTIDEPRESSANTS: A CLINICAL UPDATE

PART I

A. Use of Tricyclic Antidepressants

1) Different tricyclic antidepressants:

a) Imipramine (Tofranil)

b) Desipramine (Norpramin)

c) Amitriptyline (Elavil)

d) Nortriptyline (Aventyl)

e) Protriptyline (Vivactil)

f) Doxepin (Sinequan)

2) Efficacy: Depression - placebo 30% respond; tricyclic 60-70% respond (Overused and Underused)

3) Reported uses of tricyclic antidepressants:

a) "Biologic Depressions" (bipolar, unipolar, psychotic depression)

b) "Reactive Depressions"

c) Alcoholism

d) Chronic Pain

e) Narcotic withdrawal

f) Hyperkinesis

g) Enuresis

h) Schizoaffective schizophrenia

4. Specificity of tricyclic antidepressants:

a) Behavioral criteria

(1) anxiety and agitation vs. psychomotor retardation

b) Biologic criteria

(1) high or normal NE metabolites (MHPG) vs. low NE metabolites

c) Side effects may determine selection

d) Age

e) Genetic similarity - relatives response determines patients response and vice versa

f) Amphetamine's predictive value

5. General principles of tricyclic antidepressant use:

a) Time effects (takes 5 days - 1 month)

b) Dosage effects

(1) blood levels (drug window effect)

(2) adequate dose administration

(3) age factors (elderly requires less drug)

(4) mode of administration (oral, daily, etc.)

(5) specific drug (protriptyline requires less mgs)

c) Side effects (lethargy, etc.)

d) Maintenance therapy useful

e) Sinequan, Elavil, Tofranil - 150-300 mg/day

6. Combination therapy:

a) Lithium + a tricyclic antidepressant

b) MAOI + a tricyclic antidepressant

c) Antipsychotic + a tricyclic antidepressant

d) Methylphenidate + a tricyclic antidepressant

7) Drug-drug interactions:

Tricyclic antidepressant plus:

a) Methylphenidate

b) Sedative hypnotics (barbiturates, etc.)

c) Antianxiety agents

d) Antipsychotic agents

e) Propranolol

f) Guanethidine

g) MAOI

h) Alcohol

i) Sympathomimetics

j) Antiparkinsonian medications

8) Side effects of tricyclic antidepressants:

a) Central nervous system

(1) drowsiness, dizziness

(2) central anticholinergic syndrome

(3) seizures, ataxia, insomnia, hypomania

b) Peripheral autonomic symptoms (anticholinergic)

(1) dry mouth, palpitations, tachycardia, loss of accomodation, hypotension, constipation,

urinary retention, glaucoma, paralytic ileus

(2) use of bethanechol

c) Allergic and hypersensitivity effects

(1) jaundice

(2) agranulocytosis

d) Cardiovascular

e) Withdrawal - akathisia, nausea, headache, dizziness, muscular pain, anxiety

f) Galactorrhea

g) Parkinsonian symptoms (rare)

9) Cardiovascular effects of tricyclic antidepressants:

a) Hypertension

b) Hypotension

c) Cardiac depressant effects

d) Congestive heart failure

e) Myocardial infarction

f) Electrocardiographic effects - Therapeutic Doses

(1) increased pre-existing changes

(2) atrial fibrillation

(3) heart block (A-V block - 1st degree)

(4) right and left bundle branch block

(5) isoelectric T wave change, ST segment depression, extra systoles

g) Electrocardiographic effects - Toxic Doses: sinus tachycardia, sinus bradycardia, ventricular tachycardia, QRS segment increases, wandering pacemaker, atrial and ventricular flutter and fibrillation, A-V block, bundle branch blocks, asystole, ectopic beats

h) Sudden death - children, adults

i) Variables effecting cardiovascular effects - age, cardiac status, etc. - differential effects of various tricyclic antidepressants

j) Doxepin may be less cardiotoxic - think of MAOI here, may be safer

10) Specific treatments for tricyclic antidepressant side effects:

a) Central cholinesterase inhibitors (Physostigmine)

b) Peripheral cholinesterase inhibitors (Bethanechol)

c) Switch antidepressants

d) Give dose at night

e) Taper dose for specific withdrawal symptoms

11) Tricyclic antidepressant overdose signs:

a) Grand mal seizures

b) Cardiac failure

c) Cardiac arrthymias - early, late

d) Coma

e) Hypotension

f) Anticholinergic signs - central, peripheral

g) EKG change

h) Drugs

12) Tricyclic antidepressant overdose treatment:

a) Minimize drug absortion (emesis, charcoal)

b) Symptomatic (hydration, BP, treat seizures and hyperpyrexia, etc.)

c) Digitalis

d) Cholinesterase inhibitors (Pyridostigmine, Physostigmine)

e) Propranolol

f) Diphenylhydantoin

g) NE for hypotension

h) Cardioversion, pacemakers

PART II. NEW ANTIDEPRESSANTS

A. Second Generation Antidepressants

1. Trazodone

a. efficacy - similar to imipramine

b. therapeutic mechanism - possibly serotonergic

c. neurochemistry

d. onset of action - possibly relatively rapid

e. other uses: anxiety, schizophrenic depression, alcoholic withdrawal

f. side effects: low anticholinergic, sedative, cardiovascular, hypotension, arrhythmias, pulse rate, bradycardia

g. lethality

h. dosage schedule

2. Trimipramine

a. efficacy

b. anticholinergic side effects, sedative effects

c. does not affect REM sleep

d. cardiovascular side effects: ↑ pulse rate, His bundle effects

e. switches from depression to mania

3. Amoxapine

a. efficacy

b. weak neuroleptic

c. mostly NE uptake blocking agent

d. 2:1 dose ratio compared to imipramine

e. advantages

1) ? low anticholinergic

2) ? low cardiovascular

3) rapid onset - but try for 3 weeks

f. side effects

1) anticholinergic

2) sedative

3) stimulating

4) ? tardive dyskinesia

g. ? hypertension

4. Maprotiline

a. efficacy - like other antidepressants

b. structurally a tetracyclic drug

c. dosage - like imipramine

d. problem - drowsiness, seizures

e. ? rapid onset - but others catch up

f. side effects

1) drowsiness

2) dry mouth

3) nausea

4) anxiety

5) dizziness

6) increased QT

7) blood pressure ↓

8) pulse ↑

9) PVCs ↓

10) convulsions

11) OD is dangerous

5. Normifensine

a. novel structure

b. dopaminergic effect

c. efficacy - may be more alerting and useful in retarded depression

d. side effects

1) ↓ anticholinergic

2) no cardiovascular effects

3) low OD effects

4) low sedation

5) no ↓ in seizure threshold

6) effects on sleep

7) no potentiation of drugs