

PSYCHOPHARMACOLOGY

Based on information (written and verbal) from a seminar by
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Psychopharmacology is influenced by the DSM-IV because its descriptive, symptom-based approach to the diagnosis of mental illness allows for a better treatment response and prediction of the prognosis.

BIOLOGY OF PSYCHOPHARMACOLOGY

Body's Effect on Drugs (Pharmacokinetics)

- ∴ Absorption - The drug is broken down into the bloodstream .
- ∴ Distribution - Once absorbed, the drug is distributed to various sites of action throughout the body.
 - First Phase - Organs high in blood such as the heart, brain, kidneys, liver
 - Second Phase - Fat and muscle tissue
- ∴ Metabolism - The drug is changed into a compound which is easily excreted by the kidneys. Metabolism occurs primarily in the liver .
- ∴ Elimination from the body via the kidneys.

Drug's Effect on the Body (Pharmacodynamics)

- ∴ Pharmacological effect - The desired therapeutic effect
- ∴ Side Effects - Typically considered undesirable. Undesirable attachment to receptors in the brain .
- ∴ Allergic reactions - Immune response to medication
- ∴ Discontinuation syndrome - The response to stopping or interrupting medication treatment. Withdrawal.

Neurotransmitters

Norepinephrine

- ∴ Secreted by adrenal glands in response to stress or arousal. (fight or flight response) ∴
Regulates alertness, anxiety, tension

Serotonin

- ∴ Regulates states of consciousness, mood, anxiety
- ∴ Affects appetite, sleep, sexual behavior, states of pain

Dopamine

- ∴ Influences emotional behavior and cognition ∴
Regulates motor activity
- ∴ Regulates endocrine activity
(In Schizophrenics, there is a hyper-production of dopamine in limbic system)

Gamma amino-butyric acid - inhibitory neurotransmitters ∴

Associated with emotional balance

∴ Sleep patterns

∴ Anxiety

Glutamate

∴ Most common neurotransmitter ∴

Always excitatory

TREATMENT BASED ON DIAGNOSIS

Mood Disorders

∴ Major Depression

∴ Bipolar Disorder

∴ "Minor" Depressions: dysthymia, chronic residuals or partially recovered major depression

Core Symptoms Common to All Depressions

- Mood of sadness, despair, emptiness
- Anhedonia (loss of pleasure)
- Low self-esteem
- Apathy, low motivation, social withdrawal
- Excessive emotional sensitivity
- Negative, pessimistic thinking
- Irritability
- Suicidal ideation

Medical disorders That Can Cause Depression

•AIDS	Influenza
•Anemia	Malignancies
•Asthma	Malnutrition
•Chronic fatigue syndrome	Multiple sclerosis
•Chronic pain	Parkinson's disease
•Congestive heart failure	Pre-menstrual dysphoria
•Cushing's disease	Rheumatoid arthritis
•Diabetes	Syphilis
•Hypothyroidism	Systemic lupus
•Infectious hepatitis	Ulcerative colitis

Drugs That Can Cause Depression

Type	Brand Name
Alcohol	Various brands
Anti-anxiety	Valium Librium
Antihypertensives (for high blood pressure)	Serpasil Inderal Aldomet Ismelin sulfate Catapres Apresoline hydrochloride
Anti-parkinsonian agents	Sinemet Dopar Larodopa Symmetrel
Contraceptives	Progestin-Estrogen combinations
Corticosteroids and other hormones	Cortone Premarin, Ogen, Estrace Estraderm Provera, DepoProvera

Medication Management of Depression

Anti-depressant medication may be prescribed when there is a diagnosis of unipolar and bipolar depression, obsessive-compulsive disorder, phobias, cocaine abuse, panic disorders, bulimia nervosa and chronic pain.

Etiology of Depression and How Antidepressants Work

Neurotransmitters are released from the neuron's terminal bouton but don't make it across the synapse to the receptors of the next neuron. Instead they return to the terminal bouton. Anti-depressants block the pores so that reuptake cannot take place. Most anti-depressants currently prescribed are classified SSRIs (Selective Serotonin Re-uptake Inhibitors) or SNRIs (Selective Norepinephrine Re-uptake Inhibitors).

Types of Anti-Depressants

∴ Cyclic Anti-depressants - block the reuptake of serotonin and norepinephrine Elavil, Asendin, Anafranil, Norpramin, Pertofrane, Sinequan, Adapin, Tofranil, Ludiornil, Pamelor, Aventyl, Vivactil, Desyrel, Surmontil

Side Effects:

- Extremely dangerous in overdose. Easily used to commit suicide.
- Most tend to be sedating
- Increase the effect of alcohol
- Anticholinergic effects -regulates lens of eye, secretions, smooth muscle function, etc

Dry mouth

Blurred vision

Urinary retention

Constipation

Confusion

- Orthostatic hypotension, increase heart rate, EKG changes Weight gain - slows down metabolism of fats and carbohydrates Decreased libido

∴ Monoamine Oxidase Inhibitors (MAOIs)

MAOIs are the most effective of anti-depressants but have many side effects and restrictions. Marplan, Nardil, Parnate

Side Effects

- Hypertensive crisis (potentially serious)
- Interact with a significant number of other medications
- Orthostatic hypotension
- Activating effects may cause insomnia
- All food containing Tyramine must be avoided. MAOIs metabolize Tyramine

∴ Serotonin and Norepinephrine Reuptake Inhibitors (SSRIs & SNRIs) Prozac, Zoloft, Paxil, Celexa, Lexapro, Effexor, Cymbalta

As a class:

- More than 50% of antidepressant prescriptions are for SSRIs
- Better tolerated
- Advantage of once a day dosing
- Much safer in overdose
- Therapeutic response is not necessarily dose-dependent
- Antianxiety agents as well as antidepressant
- All are equally effective
- Similar side effects

- Recently approved for General Anxiety Disorder, Post-Traumatic Stress Disorder, Social Anxiety Disorder, Pre-Menstrual Dysphoric Disorder and Major Depressive Disorder
- SSRI "poop out" -less effective over time (9-12 months in most cases)

PROZAC

- Energizing - good for lethargic individual
- Half-life of 7 -10 days (very long)
- Six weeks to reach a stable blood level
- Prone to cause anxiety, agitation, irritability (initially feel wired)
- Interaction with other medications potentially significant

ZOLOFT

- Neither too sedating nor too energizing
- 50% of the drug excreted by the body in one day
- Stable blood levels achieved within one week
- Minimal interaction with other medications

PAXIL

- Excellent antianxiety benefit
- Unpleasant withdrawal symptoms upon abrupt discontinuation - electric shock sensation
- More fatigue, dry mouth, sweating, and constipation than other SSRIs
- Interaction with other medications potentially significant

CELEXA

- Slightly more sedating than activating
- May cause slightly less sexual dysfunction compared to other SSRIs
- Minimal interactions with other medications

LEXAPRO

- 10 mg of Lexapro daily comparable to 40 mg Celexa daily
- Claims to act faster - symptom improvement within 1-2 weeks
- No real difference between Lexapro and Celexa

EFFEXOR - (SNRI)

- "Prozac with a punch"
- Claims to be faster-acting and more effective in severe depression - as soon as 3 weeks
- Response rate linked to an increase in dosage
- Cumbersome to use because response rate linked to increase in dosage
- Risk of hypertension at doses greater than 225 mg per day - need to take blood pressure at least once a day

CYMBAL T A - same as Effexor

Serotonin Antagonist Reuptake Inhibitor (SARIs)

SERZONE

- Good antianxiety benefit
- Causes less anxiety and sleeplessness than SSRIs, Wellbutrin, and Effexor
- Low incidence of sexual side effects
- Higher the dose, the greater its antidepressant effect
- Rare reports of liver damage

Atypicals

WELLBUTRIN -

- Mechanism of action "sketchy," no effect on serotonin, modest on norepinephrine, weak dopamine activity
- Activating like Prozac
- Insomnia may be a problem
- Demonstrated effectiveness in 50-60% of those unresponsive to other agents
- Few, IF ANY, sexual side effects
- Seizure risk at doses greater than 400 mg/ day - don't use with alcohol or drug withdrawal.
- Don't know how it works but theory is that it is a dopamine reuptake inhibitor

REMERON

- Increases release of serotonin, norepinephrine
- Once a day dosing like SSRIs
- Marked sedation and weight gain
- Rare danger of white blood count destruction

Treatment Resistant Depression - has failed to respond to adequate trials of two or more antidepressants. 10-20% of subjects fall into this category. Possible causes may be:

- Incorrect diagnosis
- Inadequate dosage
- Inadequate compliance
- Substance abuse
- Wrong class of drugs prescribed

It may be necessary to augment (stimulate the receptor response) the prescribed anti-depressant by adding:

- Lithium
- Thyroid (T3)
- A stimulant
- An atypical antipsychotic such as Zyprexa •

Another antidepressant

- Typical Combinations

SSRI	+	Wellbutrin
Remeron	+	Effexor
Remeron	+	SSRI
Remeron	+	Wellbutrin
Effexor	+	Wellbutrin
Effexor	+	SSRI
Serzone	+	Wellbutrin

In some resistant cases of depression electroconvulsive treatment (ECT), trans cranial magnetic stimulation (fMS) or Vagal Nerve stimulation (VNS) may be considered. Psychotherapy has been shown to benefit the client on antidepressants.

Monotherapy is not adequate because:

- 55-65% of clients show a partial or no response to medication
- 35-45 % have active remission
- Of these, 33 % display residual symptoms

Client Education Regarding Anti-Depressants

- Stress that taking medication is *not* a sign of moral weakness
- Describe what to expect from anti-depressant medication; side effects, how to combat, tend to diminish over time
- Not habit forming
- Clinical response may take from 4-6 weeks
- If initial agent unsuccessful, others may be tried
- Take enough for long enough
- Do not abruptly discontinue

Bipolar Disorders

Typically found in creative people and in higher socio-economic groups. It is a cyclic pattern of mood, behavior, and thought processes alternating between mania and depression. The manic episode is characterized by:

- Racing thoughts
- Pressured speech
- Grandiosity
- Distractibility
- Insomnia
- Flight of ideas
- Increase in risk-taking behavior

Etiology

- Increased concentrations of Norepinephrine
- Biochemical changes in the brain cause neurons to become excited

Medical Conditions Associated with Mania

- Central Nervous System trauma, i.e., stroke
- Metabolic disorders such as hyperthyroidism
- Seizure disorders

Drugs That Can Induce Mania

- Stimulants (amphetamines)
- Antidepressants (especially tricyclic antidepressants)
- Thyroid hormones

Treatment

- Bipolar illness is viewed as a biologically-based illness. The most common treatment is pharmacological intervention with psychotherapy as an adjunct to care.
- If misdiagnosed with ADHD, taking a stimulant will make the symptoms of Bipolar worse.
- **Lithium**, the drug of choice, is a mood stabilizer used in the treatment of Bipolar Disorder. It increases the reuptake of Norepinephrine in the synapse.

Produces a normalizing effect

Slow onset of action, 5-14 days

Full stabilization may take up to several months

Requires blood level monitoring

Potentially devastating effects on the thyroid

Side effects

~ Thirst

~ Excessive urination ~

Weight gain

~ Nausea, vomiting, diarrhea

- Other mood stabilizers are the anticonvulsants **Tegretol, Depakote, Neurontin, Lamictal, Trileptal, Gabitril, Topamax**

Useful when Lithium is contraindicated

Treatment of acute mania

Seizure management

TEGRETOL

Use with those who do not respond well to Lithium or Depakote

Particularly useful with "rapid cyclers"

Demonstrated success with resistant depressions

Side effects: sedation, dizziness, drowsiness, blurred vision, incoordination, nausea, vomiting, diarrhea, abdominal pain, rashes, hives, decrease in white blood count

DEPAKOTE

First-line agent for mania

Agent of choice for "rapid cyclers"

Excellent for treating rage reactions and extreme mood instability

Sometimes used with ADHD - hyperactivity

Sometimes used for Conduct and Oppositional Defiant Disorders rage reactions

Side effects: fatigue, nausea, vomiting, indigestion, weight gain, possible poor blood clotting, possible liver disease, pancreatitis. Growing complaints of polycystic ovarian syndrome, raise of testosterone level, amenorrhea and hair growth

LAMICTAL

Excellent for "rapid cyclers"

Particularly useful in atypical depressions

Less effective for mania, more effective for the depressive end of a mood

SW111g

Side effect - severe rash

TOPAMAX

Demonstrated useful for alcohol dependence

Weight loss for some subjects

Increases insulin sensitivity, need better glucose management

Effective for seizure management but fails as mood stabilizer

Raises GABA, lowers Glutamate

Significant risks associated with medication noncompliance: a

Increased mortality risk

a Increased susceptibility to future episodes a

Decreased medication effectiveness

a Progressive worsening of symptoms

Anxiety Disorders - All anxiety disorders have in common anxiety as a symptom and avoidance as a behavior. Ask the questions, "What are you avoiding? What are you doing that you shouldn't be doing? What are you not doing that you should be doing?"

∴ Symptoms of Anxiety

- Nervousness, tension
- Poor attention and concentration
- Tachycardia
- Sweating, cold hands or feet
- Shortness of breath
- Trembling feeling
- Dizziness
- Insomnia
- Diarrhea, frequent urination or both (good sign)

∴ Symptoms of Panic Disorder

- Brief, intense surges of anxiety - Norepinephrine spike
- Often comes out of the blue
- Considerable worry as to when the next attack will occur
- Usually very responsive to medication

∴ Symptoms of Panic with Agoraphobia

- Intense fear of being in a situation where escape may be difficult or embarrassing
- Avoidance behaviors are associated with these situation
- Anxiety is always associated with entering a feared situation

∴ Symptoms of Generalized Anxiety Disorder

- Chronic low-level anxiety without panic
- Often numerous physical complaints
- Chronic worry in spite of no objective stressors
- Medication management often reduces rumination and worry
- "Worry all of the time, worry about worrying, worry when they aren't worrying"

∴ Symptoms of Obsessive Compulsive Disorder - Disorder of repetition

- Series of persistent thoughts and compulsions accompanied by shame, guilt and self-doubt
- Common obsessions: contamination and safety
- Obsessions are anxiety producing; compulsions are anxiety reducing
- Chronic condition with considerable suffering, often incapacitating
- Responds most favorably to SSRI antidepressants

∴ Symptoms of Social Phobias

- Performance anxiety
- Generalized social anxiety

∴ Symptoms of PTSD

- Persistent re-experiencing of the trauma
- Increased arousal
- Transient psychotic symptoms
- Avoidance
- Numbing

Anti-anxiety Medications -Benzodiazepines

VALIUM, LIBRIUM DALMANE, TRANXENE, KLONOPIN, RESTORIL, AMBIEN (non-benzo), SONATA (non-benzo), ATIVAN, XANAX, HALCION

Benzodiazepine Facts

Tolerance and dependence can occur
Time-limited use (1-2 weeks)
Risk of dependency associated with dose and duration of use
Considerable danger if combined with alcohol
Avoid abrupt cessation to reduce seizure risk
Excellent skeletal muscle relaxant with antispasmodic properties

Non-Benzodiazepine medications

- **BUSPAR** - "doesn't work" Only clinical use is for generalized anxiety. Sometimes used to augment SSRIs. No risk of dependence. Likely best for sober alcoholic experiencing anxiety symptoms.
- **ANTIHISTAMINES** - reduce anxiety through their sedative effects, nonhabit forming; can produce "hangover" effect.
- **INDERAL, TENORMIN (Beta-blockers)** - used to treat hypertension, block the effects of norepinephrine, reduce peripheral manifestations of anxiety, very effective for treatment of performance anxiety taken 30 min prior to talk.
- **CATAPRES** - tends to be sedating, used to treat hypertension, blocks effect of norepinephrine, useful in opiate withdrawal and alcohol withdrawal, sometimes used in treatment of ADHD for hyperactivity

Side Effects of the Anti-anxiety Medications

- Sedation
- Slurred speech
- Coordination problems
- Memory disturbance
- Disinhibition - especially with alcohol

Psychotic Disorders

∴ Brief reactive psychosis ∴

Delusional disorder

∴ Schizophrenia

∴ Schizophreniform Disorder ∴

Schizoaffective Disorder

Medical Conditions That Can Cause Psychosis

- Renal failure
- Hypoglycemia
- Vitamin deficiency
- Drug or alcohol intoxication or withdrawal
- Head injury
- Dementia, such as Alzheimer's disease

Schizophrenia is the most severe of the psychotic disorders. Its physiological pathology involves overactive dopamine neurons. Elevated levels of dopamine cause delusions, hallucination, disorganized speech and behavior. Low levels of dopamine cause blunted affect, emotional withdrawal, passivity, apathy and anhedonia.

Anti-psychotic Medications -

∴ Conventional Anti-psychotics -Dopamine antagonists (block d2 dopamine receptors in limbic system) **THORAZINE, PROLIXIN, PERMITIL, HALDOL**(for combativeness), **LOXITANE, SERENTIL, MOBAN, LID ONE, TRILAFON, ORAP, COMPAZINE, MELLARIL, NAVANE, STELAZINE.**

Side effects:

Dystonia - muscle tightening in neck and shoulder accompanied by spasms
Parkinsons - tremor, rigidity, shuffling gait, slowed movement
Akathisia - intense feeling of restlessness, thrashing
Tardive dyskinesia - involuntary facial movements, including tongue, eyes, and lips
Anticholinergic - dry mouth, blurred vision, constipation, sedation, memory
Orthostatic hypotension - drop in standing blood pressure
Weight gain - particularly with Thorazine
Grand mal seizures
Increased prolactin levels
Dose management

∴ **Atypical Agents** - block dopamine and serotonin receptors, have little or no propensity for causing EPS (extrapyramidal symptoms) or Tardive Dyskinesia, most reduce negative symptoms to a greater extent than the conventional agents.

- **CLOZARIL**

- Most efficacious, but most dangerous
 - Not a first line treatment of choice
 - FDA approval for treatment of recurrent suicidal behavior in Schizophrenics
 - Can cause agranulocytosis -low white cell count
 - Blood count monitoring necessary weekly for 6 months, then every 2 weeks.
 - Significant weight gain and very sedating
 - Linked to increased risk of Type II diabetes Potential for increasing triglycerides and cholesterol
 - Twice as effective as Risperdal and Zyprexa for treatment of Schizophrenia

- **RISPERDAL**

- Well accepted for treatment of agitation and aggression in dementia
 - Well accepted for treatment of bipolar disorders and schizophrenia
 - Anecdotal reports of use in children and treatment refractory cases
 - Minimal sedation and weight gain

- **ZYPREXA**

- First atypical antipsychotic approved for treatment of acute bipolar mania
 - Well accepted for use in bipolar disorder and schizophrenia, including difficult cases
 - Anecdotal reports of use in children and treatment resistant cases
 - Documented efficacy as an augmenting agent to SSRI antidepressants in non-psychotic, treatment-resistant major depressive disorders
 - Sedating, likely produces most weight gain compared to other antipsychotics
 - Linked to increased risk of Type II diabetes Potential for increasing triglycerides and cholesterol

- **SEROQUEL**

- Some patients respond who have failed to respond to other atypicals
 - Early studies support use in adolescents and the elderly
 - Studies support use for the management of aggressive, cognitive, and affective symptoms in schizophrenia
 - Likely the preferred antipsychotic for psychosis in Parkinson's disease
 - Essentially no EPS at any dose
 - Being used in non-psychotic insomnia

- **GEODON**

- Not first line treatment of choice
 - Least likely of the atypicals to cause weight gain
 - Least sedating
 - Potential advantages for associated anxiety and depression
 - Cardiac safety is a serious concern

- **ABILIFY**

- Mainly used as augmenting agent
 - New class of antipsychotic medication - dopamine system stabilizer (DSS)
 - Different mechanism of action from other antipsychotics

Summary of Conventional and Atypical Antipsychotics

- Conventional Agents are inexpensive, may be as effective for positive symptoms as some of the atypicals, are preferred for patients stabilized long term with acceptable side effects, and are the second-line when atypical antipsychotics fail.
- Atypical Agents are the first-line treatment of positive symptoms and negative symptoms, have fewer extrapyramidal symptoms and Tardive Dyskinesia, and have better negative system efficacy.
- Educate that relapse is common due to medication non-compliance. Discuss the "I'm cured" syndrome. Emphasize that medication is NOT a form of mind control. Explain the therapeutic effects and side effects - particularly TD.

PHARMACOTHERAPY IN SPECIAL POPULATION GROUPS

PREGNANCY

Risk Factors Associated with Medications During Pregnancy

- Teratogenesis, particularly spina bifida
- Drug effects on the growing and developing fetus
- Drug effects on labor and delivery
- Residual effects on the newborn
- Behavioral teratogenesis - developmental and expressive delays
- Drug effects on the breastfed infant - all are excreted in breast milk

Psychotropic Medication Guidelines During Pregnancy

- Antidepressants
 - ./ SSRIs and most cyclics not associated with teratogenesis ./
 - MAOIs and Remeron have not been studied extensively
 - ./ Neonate exposed to Effexor late in the third trimester may develop complications immediately upon delivery - respiratory distress
 - ./ Present in breast milk
 - ./ Neo-natal withdrawal presents as excessive crying, irritability, convulsions
- Lithium
 - ./ Established teratogen. First trimester exposure strongly associated with fetal cardiac irregularities .
 - ./ If Lithium is necessary after first trimester, dosage adjustments are necessary due to pregnancy-induced kidney function changes .
 - ./ Neonatal effects include impaired respiration, EKG and heart rate abnormalities, and renal impairment .
 - ./ Significant concentrations in breast milk. Nursing contraindicated
- Antipsychotics
 - ./ Establish lowest effective dose possible
 - ./ Potential short-term abnormal neonatal motor activity ./
 - Possible alternative to Lithium in mania
 - ./ Present in breast milk
 - ./ Haldol and Zyprexa are safe during pregnancy for management of acute marua
- Anticonvulsants
 - ./ Tegretol is a probable teratogen
 - ./ Depakote is an established teratogen ./
 - Both found in breast milk

- Benzodiazepines

- ./ Avoid use in first trimester
- ./ Use Klonopin if benzodiazepines are absolutely indicated
- ./ Neonatal central nervous system depression, drug accumulation, and withdrawal symptoms possible
- ./ Excreted in breast milk Produces drowsiness, failure to thrive in infant

CHILDREN AND ADOLESCENTS

Mood Disorders

- Major depression is diagnosable in children and adolescents using the same criteria as used for adults
- Children and adolescents do not spontaneously report symptoms
- Elicit information regarding symptoms from parents or caretakers
- Bipolar adolescents are common and look similar to adult presentations. Differences are that children tend to be rapid cyclers, have shorter episodes and present with mixed symptoms.
- Prozac was approved in January 2003 for the treatment of major depressive disorder and obsessive compulsive disorder in children and adolescents
- Dosage ranges usually 50% of adult dose

Anxiety Disorders

- Medication management studies are virtually non-existent and inconclusive

Attention Deficit Hyperactivity Disorder

- Four to nine times more common in boys among children
- Onset by age 7-8
- 75% of children treated with stimulants elicit a positive response
- Common side effects of stimulants: insomnia, poor appetite, weight loss, nausea, GI upset, tics due to rising level of dopamine
- 70% of children with ADD go on to experience ADD symptoms in adolescence and adulthood

ADHD Etiology

Possible causes

- Predominantly hyperactive and impulsive symptoms may be due to dopamine dysfunction
- Genetic component - increased risk for ADHD in first degree relatives
- Dietary factors - vitamin deficiencies, food additives, and food allergies
- Prefrontal cortex subjected to under-arousal
- Low iron levels are associated with ADHD

Medications - Stimulants arouse areas of the brain that are under-aroused. Increased dopamine helps with concentration.

- WELLBUTRIN -75-100 mg, used to augment
- WELLBUTRIN SR - 100 mg - 150 mg
- DEXEDRINE - 5-10 mg
- ADDERALL - 5-10 mg
- ADDERALL XR- 10, 20, 30 mg
- DEPAKOTE, DEPAKOTE, SPRINKLES, DEPAKOTE ER -125,250,500 mg
used in cases where child is very hyperactive
- RITALIN - 5, 10, 20 mg
- RITALIN SR - 20 mg
- METHYLIN ER - 10, 20 mg •
- RITALIN LA -10,20 mg
- METADATE CD-20mg
- CONCERT A -18, 27, 36, 54 mg
- EFFEXOR - used to augment
- EFFEXOR XR - used to augment
- STRATTERA -10,18 mg (non-stimulant) efficacy more significant in adults

Children do best when levels of dopamine are on the rise. Regular release stimulant gives only one peak. Continuous release (SR, ER) last 8 hours but there is no peak. Bi-phasic release (LA, CD, Concerta) gives 2 peaks.

With stimulants, dosing after noon is contraindicated. Weight loss is likely to be transient. Claims regarding growth retardation are unfounded.