UNIVERSITY OF CALIFORNIA
SAN FRANCISCO MEDICAL CENTER

BERKELEY • DAVIS • IRVINE • LOS ANGELES • RIVERSIDE • SAN DIEGO • SAN FRANCISCO
SANTA BARBARA • SANTA CRUZ

UNIVERSITY OF CALIFORNIA HOSPITALS
SAN FRANCISCO, CALIFORNIA 94122

Child Study Unit, 546-C
Department of Pediatrics
January 9, 1970

Ronald S. Lipman, Ph.D.
Chief, Clinical Studies Section
Psychopharmacology Research Branch
National Institute of Mental Health
5454 Wisconsin Avenue
Chevy Chase, Maryland 20015

Dear Ron,

Enclosed is a summary of my report on side effects to which I have added from material gratefully received from Barbara Fish and Rachel Gittelman-Klein. I will need assistance from Keith regarding the rating scales for behavioral side effects since there would seem to be much overlap with target symptoms. It may be that the same behavioral rating forms for parents and teachers can cover both? The same question comes up relative to baseline determinations of child, parent, and teacher's attitude and role.

During lunch at our November meeting, one of your young colleagues whose name I can't remember (he has been doing some studies in San Francisco) mentioned a study he had made of physician's attitudes and suggested his studies and forms might be useful to this project. Could you please send me his name or any material he may have available?

I am also enclosing a questionnaire we used in a follow-up study of children with delayed language development. It may be of some use in formulating the history form. We find parents have great difficulty remembering ages for developmental milestones but do remember differences from siblings relative to development and behavior. In our study, even though these parents had been very concerned about the child's speech development, the majority of them were unable to remember when the child said his first word, phrases, or short sentences but could remember whether these were earlier or later compared to siblings.

I will welcome comments on any of the summary from any of the group, particularly regarding item B-7 of my summary. I would also welcome suggestions regarding the physical side effects list--what items might be eliminated or left for the "others" category and what items should be added, and comments regarding which rating scales (see page 7) need to be devised.

Sincerely,

Helen

Helen Gofman, M.D.
Director, Child Study Unit
Associate Professor in Pediatrics

Encls.

HG:jmn

Pediatric Psychopharmacology Conference
November 13-14, 1969 N.I.M.H. Bethesda, Maryland

Report on Treatment Emergent Symptoms (Side effects)

Helen Gofman, M.D.

Attitudes

The following items should be considered in any study of effects (desirable or nondesirable) of psychotropic medications in children. Many of the factors that may influence the reports of drug response will also influence the reporting of side effects. Base line information and ongoing assessment re these factors is essential in planning this study and in devising rating sheets to evaluate the target symptoms as well as side effects.

A. Is the prescribed medication being taken by the child?

Tests are needed to ascertain the dosage actually being taken. Ideally blood levels or urine levels might give most reliable information. For many studies this may not be possible. Rating sheets should be devised for base line and regular assessment of dosage taken and the following should be considered in their construction:

1. Can the child take the medication or placebo in the form prescribed? An actual demonstration might be required.

2. Note amount of medication missing from the bottle on each visit.

3. Assume that some of the doses will be missed and devise questions that imply permission for these lapses in order to ascertain as accurately as possible the amount given as the study proceeds.

4. Determine who gives the child the medication. Is it the individual being questioned at repeated evaluations of the child? Is it the same individual consistently during the day or week--or many different adults who may prejudice the study by their bias (unknown to the investigator) or by poor reliability.

5. Are other medications being taken that are not part of the study?

6. Interval illness, infection or injury (more common with children) may influence side effects and target symptoms, the use of other medication, and/or the discontinuance of the prescribed medication.

Baseline assessments of attitudes of those participating in the study will be important in the total evaluation of results. These individuals include the child, his parent or caretakers, physicians, teachers or others intimately involved with the child. Baseline rating scales and periodic interval rating scales of their attitudes should be an essential part of the study.

B. Physician's attitude and role.

Factors that might be considered:

1. Experience in caring for children, especially treating their behavioral and emotional problems.

2. Previous experience using psychotropic drugs with adults or children, whether positive or negative. (It would be interesting to devise some studies of the same medications and similar populations, but with physicians with positive versus negative attitudes toward psychotropic drugs.)

3. Attitude toward psychotropic drugs, behavior modification, psychotherapy in relation to these problems.

4. Previous experience using psychotropic medication with own children or children of close friends or relatives and whether positive or negative.

5. Physicians own expectations from the study.

6. Why is he carrying out study? (What is in it for him?)

7. Orienting and training the physician in conducting the study.
   a) Explanation of study to families. Will an attempt be made to achieve some consistency in these explanations in terms of purpose, design of study, use of placebos, warning re side effects etc? Will an effort be made to note time spent in orientation of subjects?
   b) Procedure for follow-up visits. Consistency in questions asked, time spent with subjects.
   c) Procedures for other than subject contacts. Discussion, explanation and time spent with teacher, nurse, etc.
   d) Time interval between visits.
   e) Length of study.

8. His attitude toward subject and family.
   a) How long has he known them?
   b) Previous experience (+ or -) with child.
   c) His evaluation of parents and sibs.
   d) Previous attempts in treating child.

9. Consistency of physician, subject contact. Same or different physician?

C. Child's attitude and role.

D. Parent's attitude and role.

E. Teacher's attitude and role.

Most of the following items will apply to all three of the above and should be considered in divising baseline and follow-up rating scales.

1. Severity and duration of child's symptoms.

2. Degree of stress caused by symptoms.

3. Previous experience with psychotropic medications.
   a) What have heard from reading, TV, other parents, professionals?
   b) Have they known a child treated with these medications--positive or negative effect?
   c) Experience with own child and medication.

4. Expectations or hopes ré effect of medication.

5. Fears ré effects of medication.

6. Feelings ré participating in study.

7. Understanding of why medication is being given.

8. Relationship with investigator.

Side Effects

Rating scales for side effects should provide for symptoms, intensity, and in many cases variations or consistency in relationship to time, changes in environment, changes in routine. This may be important particularly in evaluating adverse behavioral effects as well as target symptoms.

Side effects--Mainly Physical

The following symptoms and physical findings should be assessed in the baseline studies and reassessed on follow-up visits with the investigator. Some of these symptoms might be compiled in a rating scale for parents to use daily or weekly.

The symptoms listed will need to be reduced to fewer general categories on the final record form. To obtain the final ratings, observations will need to be made and specific questions with inter investigator consistency will need to be asked about the following:

General
Height
Weight
Temperature
Pulse
Respiratory rate
Blood pressure

Central Nervous System
Tremor
Rigidity
Ataxia
Poor balance
Incoordination
Weakness
Atonia
Dystonic symptoms (jaw-tongue face-neck syndrome)
- Difficulty swallowing
- Difficulty speaking
- Spasmodic movements of tongue, lips, mandible and neck
- Torticollis
- Opisthotonus
- Muscle twitching
- Oculogyric spasms

Inability to sit still--muscle restlessness
Masked facies
Speech changes--indistinct
monotonous
Drooling
Parathesias
Seizure activity

Abnormal Laboratory Findings
Hematological findings
Liver function
Urinalysis
?Blood chemistries

Interval History
Illness
Injury
Changed routine
Changed environment

Gastro intestinal and/or autonomic
Weight loss
Weight gain
Increased appetite
Decreased appetite
Mouth (mucosa, tongue, lip) dryness
Bad taste
Increased salivation
Stomach ache
Abdominal cramps
Nausea
Vomiting
Constipation
Diarrhea

Cardiovascular-respiratory and/or autonomic
Tachycardia
Bradycardia
Cardiac arrythmias
Increased blood pressure
Decreased blood pressure
Chest pain
Dypsnea
Nasal Congestion
Nose bleeds
Fainting--blackouts

Genito--urinary and/or autonomic
Urinary frequency
Urinary retention
Bedwetting
Decreased bedwetting
Daytime incontinence
Painful urination

Occular
Pupils--size
Retinal changes
Conjunctival injection, jaundice
Itching--tearing
Photosensitivity
Blurred vision
Extraoccular muscle imbalance
Nystagmus

Skin and/or autonomic and/or idiosyncratic
Pallor
Flushing
Mottling
Sweating
Rash
Urticaria
Pruritis
Skin pigmentation
Jaundice
Purpura

Miscellaneous
Headache
Dizziness
Tiredness
Non-Specific somatic complaints

Side Effects--Behavioral

There may be some overlap in assessing behavioral side effects and target symptoms. Some of the behavioral side effects may be positive or negative and may or may not be target symptoms, but should be noted in these studies. Rating scales for parents, teachers and ? subject will be needed here.

Adverse Behavior Effects	Positive Behavior Effects
Insomnia--Can't get to sleep	Improved sleep
Restless sleep	
Insufficient sleep	
Nightmares	
Drowsiness	More alert
Daydreaming	
Apathy	
Withdrawal	More communicative
Fatigue	More energetic
Sadness, unhappiness	Improved mood
Restlessness--motor	Less restless
Goes from one thing to another	Finishes tasks
Irritability, jitteriness, tenseness	Calmer
Decreased stress tolerance	
Catastrophic reaction to stress	Handles stress better
Catastrophic reaction to failure	Handles failure better
Catastrophic reaction to new situations	Handles new situations better
Temper tantrums with frustration	More even tempered
Temper tantrums without frustration	More even tempered with frustration
Destructiveness	Less destructive
Negativism	More positive mood
Impersonal	More concerned with people around him
Cruelty	
Impulsiveness	Plans ahead
Unpredictability	Requires less supervision
Fool hardiness	More cautious
Mood swings, increased lability	More even disposition
Anxiety, fearfulness	Less fearful, anxious
Oversensitivity	
Weepiness, crying spells	
Memory lapses, impairment	Improved memory

Adverse Behavior Effects (cont.)	Positive Behavior Effects (cont.
Confusional states	More aware of surroundings
Hallucinations	
Perseveration	More tractable
Repetitive motor activity-- rocking, head banging	

Summary

The following rating sheets may need to be devised for baseline and follow-up information relative to side effects:

1. Ascertaining actual medication intake. (Baseline information and periodic assessment.)
2. Physician's attitude and role
3. Child's attitude and role
4. Parent's attitude and role
5. Teacher's attitude and role
6. Side effects--physical (?Interval rating sheets for parents, too.)
7. Side effects--behavioral (interval rating sheets for parents, interval rating sheets for teacher)

✓ Methylphenidate (Ritalin)
✓ Elavil Duaner
✓ Chlorpromazine (Thorazine)
✓ thioridazine (Mellaril)
Diphenhydramine (Benadryl)
✓ Imipramine (Tofranil)
✓ nortriptyline (Aventyl)

✓ Perphenazine (Trilafon) tricyclic.
✓ Trifluoperazine (Stelazine) antidepressants
✓ Flupheazine (Prolixin)
✓ Prochlorperazine (Compazine)
✓ Chlorprothixine (Taractan)
✓ Haldol (Haldol)
✓ Amitriptyline (Elavil)

✓ Phenelzine MAO (

✓ Chlordiazepoxide (Librium)
✓ Diazepam (Valium)
Meprobamate (Miltown)
Magnesium Pimaline (Cylert)

	Chlorpromazine	Thioridazine	Fluphenazine	Prochlorperazine	Chlorprothixene	Haloperidol	Amitriptyline	Imipramine	Nortriptyline	Phenelzine	Chlordiazepoxide	Diazepam	Meprobamate	Amphetamines	Methylphenidate	Diuril	Magnesium pemoline	Trifluoperazine	Perphenazine
Tremor	X																	X	X
Rigidity	X																	X	X
Ataxia		X									X		X						
Poor balance												X							
Incoordination																			
Weakness																			
Atonia			X	X	X	X												X	X
Dystonic symptoms	X													X	X				
Motor restlessness																			
Masked facies																			
Speech changes	X																		
Drooling																			
Parkinsonism			X																
Seizure activity	X																		
Blood dyscrasias														X					
Weight loss																			
Weight gain																			
> appetite							X							X	X				
< appetite								X											
Mouth dryness	X																		
Bad taste																			
> salivation														X					
Stomach ache	X																		
Abdominal cramps														X	X	X			
Nausea																			
Vomiting																			
Constipation														X					
Diarrhea	X																		

X: Dilaudid stat

	Chlorpromazine	Thioridazine	Fluphenazine	Prochlorperazine	Chlorprothixene	Haloperidol	Amitriptyline	Imipramine	Nortriptyline	Phenelzine	Chlordiazepoxide	Diazepam	Meprobamate	Aspirin	Methylphenidate	Demerol	Ergotamine tartrate	Trifluoperazine	Quinidine
Tachycardia																			
Bradycardia																			
Arrythmias																			
↑ BP																			
↓ BP												X							
Chest pain																			
Dyspnea																			
N&V/cramps		X																	
Nose bleeds		X																	
Fainting																			
Urinary Retent																			
" Freq.																			
Bedwetting																			
↓ "																			
Daytime dreamt																			
Painful Muscles																			X
Pupil change																			
Retinal change																			
Eye/Eyelid Injection										X									
" Jaundice							X												
Itching/Rash																			
Photosens.																			
Blurred Vision								X										X	
EOM Imbal																		X	
Nystagmus																			
Allergic reaction																	X		

Perphenazine	Trifluoperazine	Magnesium pemoline	Deanol	Methylphenidate	Amphetamine	Meprobamate	Diazepam	Chlordiazepoxide	Phenelzine	Nortriptyline	Imipramine	Amitriptyline	Haloperidol	Chlorprothixene	Prochlorperazine	Fluphenazine	Thioridazine	Chlorpromazine	
					x														Pallor
																			Flushing
																			Mottling
																			Sweating
x						x					x						x	x	Rash
																x		x	Urticaria
																			Pruritus
																		x	Photosensitivity
																			Skin pigment
																			Jaundice
																			Purpura
																	x		Headache
					x		x	x				x					x		Dizziness
												x						x	Tiredness
																		x	Depression
				x	x			x	x					x					Insomnia
x	x					x	x	x	x			x	x	x		x	x	x	Drowsiness
x																	x	x	Lethargy
x	x				x		x										x	x	Excitability
					x							x							Weepiness
																			repetitive activity
																		x	Confusion
									x										agitation
																			Catastrophic reaction
x					x			x	x		x	x					x	x	Irritability
								x										x	Depression
				x									x						Hallucinations
													x						Muscular spasms

* reduces psychomotor excitement + disorganized psychotic behavior.
** + ?? activating effect

Tranquilizers

Major

Phenothiazine derivatives

see separate page

* Chlorpromazine (Thorazine) (30-1000 mgm) (0.6 mg/lb) } open chain

Promazine (Sparine) (weaker) + < toxic - ?? higher incidence seizures (30-1000 mgm) dimethylamine

Triflupromazine (Vesprin) > + > toxic (20-200 mgm)

agranulocytosis
> extrapyramidal effects
Irritability
agitation
Dyskinesia
less impaired children

Prochlorperazine (Compazine) ← little + effect
> + > toxic to children
5 x 10 x chlorpromazine (5-200 mgm)

Perphenazine (Trilafon) most toxic + ?? effective
> + > toxic 5 x 10 x chlorpromazine (??)

Piperazine N  N

→ side chain

** Trifluoperazine (Stelazine) ← tolerated well by children - apathetic or schiz
> + > toxic 20-100 x chlorpromazine (1-80 mgm)
c < dystonia) may > alertness and motor drive. Fish

Fluphenazine HCl (Prolixin) - long acting
100 x potent >> + > toxic than (0.5- 10 mgm)

? reversible T wave changes

* Thioridazine (Mellaril) long acting Piperadine
> toxic (some say < toxic) - eye changes retinitis pigmentosa
(15-500 mgm) 0.6/lb accumulates - 2 in 3-4 da
corneal-lenticular opacities
Safe for children - greater dysfunction

Thioxanthene Derivatives I Chlorprothixene HCl (Taractan) - like chlorpromazine

Rauwolfia Alkaloids

for severely schizophrenic only

Reserpine (Serpasil) - stim parasymp inhib symp (0.1 - 10 mgm)

{ lethargy
insomnia
nightmares
Parkinsonism
Convulsions
GI ulcer
diarrhea
nasal congest.
↑ BP

Butyrophenones

Haloperidol (Haldol) still investigational
useful in Gille de la Tourette's Syndrome { EPS
psychomotor agitation drowsiness

Tranquilizers

Major

Phenothiazine Derivatives

a) schizophrenia, autism
b) ? hyperkinesis
< distractive or aggressive behav.

Chlorpromazine (Thorazine)

depresses reticular system, brain stem
inhibits deamination of serotonin
interferes c nor epi → < symp. discharge
partly destroyed - liver

? infertility

Side effects

sluggishness
weakness, apathy, chilliness
motor restlessness
tremors
torsion spasms } less in children
Parkinsonism }
seizures

rare
- melanosis - skin
- retina, cornea, lens
- dyskinesia

Toxicity

- Constipation
- orthostatic hypotension
- dermatitis - photosensitivity
- amenorrhea
- urinary retention
- fluid retention
- weight gain
- EKG changes

Rare

- jaundice
- aplastic anemia
- agranulocytosis
- asthma

Antidepressants

?? nsc

Monoamine Oxidase Inhibitors (MAOI) > nor epi 5 HT

[rarely indicated in children] Phenelzine

Iproniazid (Marsilid)
~~very toxic~~

Dont use c MAOI or benzodiazepines

Iminodibenzyl Derivatives > nor epi 5. H. T

(tricyclic antidepressants)

Imipramine (Tofranil)
(10 - 200 mgm)

Nortriptyline (Averityl)
10 - 200 mgm)

Atropine like side effect
dry mouth
constipation
tachycardia
blurred vision
drowsiness
agitation
urinary retention
eosinophilia
rare agranulocytosis
coarse tremors
simple spasms

like phenothiazines
onset of action is slow - requires several days to weeks to establish drug effect.

Amitriptyline (Elavil) > drowsiness rare convulsions

Minor Stimulants (Whitehall - Mild Anti-depressants)

Excitatory action - retic activating system

Amphetamines -

Amphetamine (Benzedrine)
Dextro " (Dexedrine)
Whitehall (2.5 - 60.0 mgm)
Weaver 0.1 mgm/lb
Mallinckrodt (2.5 - 40 mgm)

Methamphetamine (Methedrine)
(2.5 - 30 mgm)

- mouth dryness
- anorexia
- wgt loss
- insomnia
- irritability
- palpitation, tachycardia
- sweating
- GI disturbances
- stomache
- tremor

Piperidine derivatives

Methyl phenidate (Ritalin)
Whitehall (10 + 80 mgm)
Weaver 0.7 mgm/lb
Mallinckrodt 5 - 200 mgm (0.25 mgm/kilo → 2 mgm/kilo)

- acts on RAS
- improves coord
- narcolepsy
- agitation
- insomnia
- GI disturbance
- occasional amnesia
- rash
- dizziness
- chest pains
- rare cardiac arrythmias
- facial twitching, speech difficulty & tongue & lip movement.

Tertiary Amines - ? acetyl choline potentiation

Deanol (Deaner)
(25 - 300 mgm)

- muscular tension
- twitching
- insomnia
- headaches
- pruritis
- rash
- constipation
- may ↑ seizures

Magnesium Pemoline (Cylert)
? improves memory.

Tranquillizers

Minor (cont)

Glyceral derivatives, propanediol derivatives

Meprobamate (Miltown, Equanil)
? if better than phenobarb
(200-2400 mgm) (seizures c withdrawal)

{ fever, G.I., rash, ↓ BP, leucopenia, purpura, ataxia

Benzodiazepines - act on limbic system, thalamus + hypothalamus
anti conv. action

> potent tranquillizer than above

chlordiazepoxide (Librium)
(10 - 300 mgm)

diazepam (Valium).
(2 - 40 mgm) useful IV in status epilepticus

} drowsiness + fatigue, ataxia, muscle weakness, hypotension, constipation, incontinence, rash, blood dyscrasias, edema, jaundice (rare), drowsiness

withdrawal symptoms.
paradoxical rage reactions
confusion

Diphenylmethane derivatives (Anticholinergic)

Diphenhydramine (Benadryl)
caution c seizures
(25-400 mgm)

Hydroxyzine HCl (Atarax - Vistaril)
Antihistamine
(20-1000 mgm)

} drowsiness
[reverses dystonic syndrome caused by major tranquillizers]
dizziness
dry mouth
rare over excitation

✓ mentioned
x > common
I rare

	Anorexia	Wgt loss	Mouth dryness	night mares Insomnia	agitation > irritab.	tachy-cardia	Sweating	tremor	dizziness	muscle twitching	ataxia
1 Amphetamines	x ✓	x	✓	x	x	✓	✓	✓			
2 methyl phenidate				x	x				✓		
3 deanol				x						✓	
4 chlorpromazine }					✓			✓			
5 & other phenothiazine deriv. }											
6 reserpine.				✓							
7. diphenhydramine											
8 meprobamate											✓
9 chlordiazepoxide											✓
10 diazepam											✓
11.											

	Parkinsonism	jaw tongue face neck syndrome	nasal congest.)	seizures	↑BP	↓BP	urinary retention	fluid retention	EKG change	wgt gain	fatigue	apathy	drowsiness lethargy
1													
2		✓											
3				✓									
4	I			I		✓	✓	✓	✓	✓		✓	✓
5	✓												
6	✓		✓	✓	✓								✓
7				✓									✓
8						✓							
9						✓		✓			✓		✓
10						✓		✓			✓		✓

	GI disturbance	stomach ache	constipation	diarrhea	rash	pruritis	dermatitis photo sensitivity	blood dyscrasia	jaundice	chest pain	cardiac arrythmias	head ache	asthma
1	✓	✓											
2	✓	✓			✓					✓	I		
3			✓		✓	✓						✓	
4			✓				✓ melanosis	II	I				I
5													
6	ulcer			✓									
7													
8	✓				✓			leukopenia purpura					
9			✓	incont.	✓			✓	✓				
10			✓	incont.	✓			✓	✓				