A Critical Look at Medication Management Issues in Alzheimer's Disease

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Dementia: Alzheimer's Disease

Educational Objectives

- 1. Define the role for cholinesterase inhibitors in the management of Alzheimer's disease, Lewy Body dementia, Frontal Temporal Lobe dementia.
- 2. Name three common side effects of atypical antipsychotic drugs.
- 3. Construct a pharmacological treatment plan for a 77-year-old patient diagnosed with Alzheimer's disease and hallucinations.
- 4. Describe the role for antipsychotic, antidepressant, mood stabilizers and benzodiazepines in the management of psychiatric behavior problems related to Alzheimer's disease.
- 5. Cite three potential drug or disease interactions with cholinesterase inhibitors.

Disclosures

Pfizer	Speakers Bureau
Forest	Speakers Bureau
Novartis	Speakers Bureau
Rx Consultant	Associate Editor
WindChime	Consultant
HGA HealthCare	Consultant
Elder Care Specialist	Consultant

Risk Factors Linked to AD

- Over 65 years of age and increases with age
- female
- Head injury
- Factors associated with DM, HTN, CVD
- Genetic: family history, specific chromosome mutations
- History of heavy cigarette smoking

The Many Faces of Dementia

- Alzheimer's Disease
- Vascular: Multi-infarct
- FrontalTemporal Lobe dementia (FTD) and Pick's disease
- Lewy Body Dementia
- Progressive Supranuclear Palsy
- Corticobasal Degeneration
- Primary Progressive Aphasia
- Huntington's disease
- Dementia Associated with Parkinson's, AIDS etc.
- Creutzfeldt-Jakob

Basic History of Illness

- Lewy Body Dementia
  Hallucinations, Parkinsonism, Visual Spatial +/-
- Frontotemporal Dementia
  - Changes in personality, lack of impulse control
    Dietary changes, compulsive behavior, **(-)** empathy
- Vascular Dementia
  - Progressive memory impairment, relatively rapid onset
    History of DM, HTN, CVA, CAD

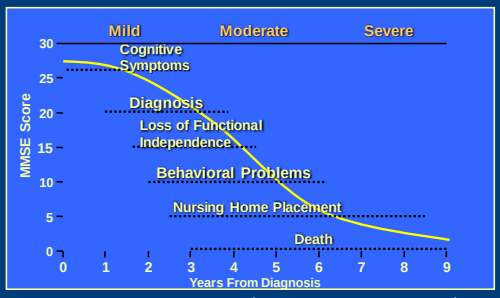
Basic History cont.

- Alzheimer's Disease
  - Development of multiple cognitive deficits manifested by both memory impairment and 1 or more of the following cognitive disturbances:

    aphasia, apraxia, agnosia, or disturbance in executive functioning.*

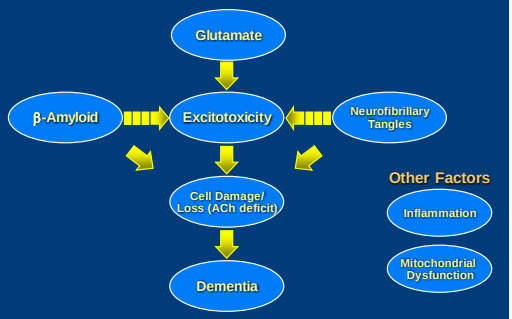
*DSM IV-R

Clinical Disease Progression

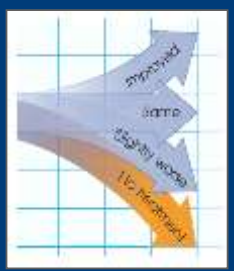


Reprinted from *Clinical Diagnosis and Management of Alzheimer's Disease*, H Feldman and S Gracon; Alzheimer's Disease: symptomatic drugs under development, pages 239-259, copyright 1996, with permission from Elsevier.

Pathophysiologic Hypothesis of AD



Goals of Therapy



Improved

Unchanged (symptoms are no better or worse)

Slightly worse, but better than expected with no treatment

With no treatment, the patient would be expected to decline more rapidly

Take a Complete Medication History

- Prescription Drugs
- Non-Prescription Drugs (ibuprofen, aspirin, etc.)
- Alternative treatments (vitamins, herbals, etc.)
- Social Drugs (alcohol, nicotine, caffeine)
- "Other Social Drugs" (marijuana, cocaine, etc.)
- Immunizations (influenza, pneumonia, etc.)
- Allergies (drugs, foods, etc.)
- What works, what doesn't't (e.g., pain meds)
- Medication Adherence

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#1 “I only have two glasses of wine with dinner”

#2 “I only have a cocktail at social gatherings”

#3 “I don’t drink”

- Question
  - How large are the glasses?
  - Tell me about your social gatherings
  - Did you ever drink alcohol?

“biopsy the medicine cabinet”

GH 73 year old male retired chemical physicist with a recent diagnosis of mild Alzheimer’s Disease

- CC: GH reports “ I have no get up and go”. Spouse reports, “ He was very anxious, even before the AD diagnosis. We would like to start the Alzheimer’s medication”
- BP 120/80 HR 72 MMSE: 24 GDS: 2/30
- ADLS/IADLS: unable to select clothes, dresses with assistance, can no longer shop for groceries, needs assistance in preparing meals.
- Meds: Atenolol 25 mg daily, HCTZ 25 mg daily, alprazolam 0.25 mg orally four times daily
- OTC:ASA 81 mg daily, Huperzine A 200 mcg twice daily, Mind Matrix, 3 tablets daily (started 7 days ago)

Mind Matrix Ingredients

- Gingko Biloba
- Acetyl L Carnitine
- St. John's Wort
- L Glutamine
- DMAE (diethylaminoethanol)
- Bacopin
- Vinpocetin
- Phosphatidylserine

RX galantamine ER 8 mg po once daily in the AM

- " I have severe nausea and diarrhea"
- " My anxiety has suddenly greatly increased"
- " I seem to be bruising much more than usual. "
- " This new medicine you prescribed has terrible side effects" " Can I stop it?"

Drugs and Cognitive Impairment

- Common cause of potentially reversible cognitive impairment
- Demented patients are particularly prone to delirium from drugs
- Benzodiazepines, ETOH,
- Anticholinergic drugs are common offenders (TCAs, diphenyhydramine, many others)
- Other offenders cimetidine,ranitiddine,famotidine, steroids

Medical Letter 2000 Drug Safety 1999 Drugs and Aging 1999

Cholinesterase Inhibitors and Anticholinergic Drug Interactions

- Benztropine
- Oxybutynin (Ditropan)
- Tolterodine (Detrol)
- Diphenhydramine
- Cyclobenzaprine
- Belladonna alkaloids
- Amitriptyline, Doxepin, Imipramine

Tune L. Anticholinergic delirium: Assessing the role of anticholinergic burden in the elderly.Current Psychosis and Therapeutics Reports March 2004;2 (1):33-36

Additional Anticholinergics

- Nortriptyline
- Paroxetine
- Olanzapine
- Hydroxyzine
- Cetirizine (Zirtec)
- Doxylamine(Unisom)
- Chlorpheniramine
- Brompheniramine

Sink K, Thomas J et al. Dual Use of bladder anticholinergics and cholinesterase inhibitors:long term functional and cognitive outcomes.JAGS; May 2008 (56):847

Cholinesterase Inhibitors

Year	1993	1996	2000	2001
Drug	Tacrine	Aricept	Exelon	Razadyne
Action	reversible	reversible	Pseudo irreversible	reversible
Class	Acridine	Piper-idine	carbamat e	Phenanthrene alkaloid
AchE	yes	yes	yes	yes
BuChE	yes	minimal	yes	minimal

Donepezil Summary

- Donepezil (5 and 10 mg and 23 mg SR) may improve cognition and global function in patients with mild, moderate and severe AD
- Long-term efficacy is maintained for up to 50 weeks in select patients
- ADL may be partially maintained by donepezil
- Donepezil is generally safe and generally well tolerated

Rivastigmine Summary

- Rivastigmine (6–12 mg/day or 4.6 to 9.5 mg/day patch) may improve cognition and global function in patients with mild-to-moderate AD
- Positive effects on ADL have been observed in some studies
- Rivastigmine is generally safe and well tolerated, although cholinergic side effects occur at high doses*
  - *fewer side effects with patch

Galantamine (Razadyne®) summary

- Galantamine (16 to 24 mg/day) Competitive inhibition of acetylcholinesterase
  - Allosteric modulation of presynaptic and postsynaptic nicotinic receptors[2]
- Galantamine may improve aspects of AD (e.g, cognition, behavior, function)
- Galantamine is generally well tolerated
  - galantamine can be purchased as an herbal OTC
  - Dose in Moderate Renal Impairment: 16 mg/ day

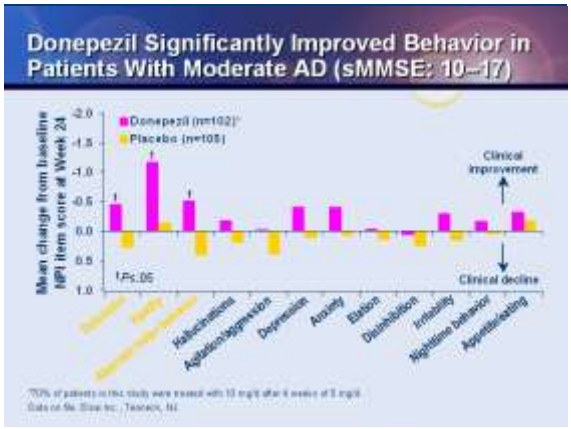
Cholinesterase Inhibitors and Neuropsychiatriatric Symptoms*

Source	N	Medication	Days
Morris et al	408	metrifonate	168
Dubois et al	605	metrifonate	168
Raskind et al	264	metrifonate	182
Tariot et al	978	galantamine	150
Rockwood et al	386	galantamine	90
Farlow et al	468	tacrine	84
Knapp et al	653	tacrine	210
Moller et al	181	physostigmine	168
Zemian et al	309	velnacrine	42
Winblad et al	286	donepezil	365
Jann	395	metrifonate	42
Becker	180	metrifonate	180

efficacy of cholinesterase inhibitors in the treatment of neuropsyciatric symptoms and functional impairment in Alzheimer disease. JAMA January 8, , 2003. Trinh NH, Hoblyn J, Monhanty S, Yaffe K.

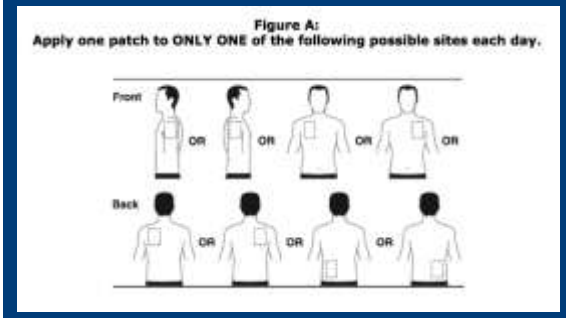
*Using NPI or ADAS-noncog

+ tacrine and metrifonate studiesx3*



Dosing Tips

- Nausea or Diarrhea Reduce dose and restart titration
- Titrate slowly
- Do not increase donepezil 10 mg daily abruptly to 23 mg dose.
- Divide dose (twice daily)
- GI SE? Consider starting memantine first
  - Titrate memantine up to max dose and then start cholinesterase inhibitor



Drug Interactions: AChEi

- Highly Anticholinergic Drugs
  - Belladonna Alkaloids
  - Tricyclic Antidepressants
  - First generation Antihistamines
  - Many skeletal muscle relaxants
  - Drugs to Tx urinary incontinence
  - Many Antipsychotic Drugs
  - Some antiarrythimics (disopyramide)

Drug Interactions: AChEI's

- Succinylcholine-type or cholinergic agonists
- Ketoconazole*
- Quinidine*
- Erythromycin*
- Paroxetine*
- Cimetidine*

* Either not clinically significant or unknown clinical significance

Optimizing AChEi Drug Therapy

- Do not expect immediate response
- Counsel patient-caregivers on expectations.
- Monitor medication adherence
- A six month trial
- Consider adding memantine
- Titrate to maximal tolerated dose
- Avoid anticholinergic drug interactions

AChEi Side Effects

- Nausea and/or Vomiting
- Diarrhea
- Disturbing Dreams
- Muscle cramps or pain
- Syncope
- Hypomania
- Weight loss
- Surgical Issues - interactions

Contraindications* and Precautions for AChEi ' s

- Hypersensitivity to the ACEhI*
- Cardiac Conduction Conditions
- Symptomatic Bradycardia
- Severely Impaired Renal or Hepatic function

Pros and Cons of AChEi Therapy

- Pro
  - Some patients will benefit, better results in LBD vs AD
  - May reduce need for psychoactive drugs
  - Opportunity to improve ADL's and IDL's
  - Reduction in caregiver time
  - Reduction in Apathy, improved social awareness/interaction, improve ADLS

Cons

- Side effects may be troublesome
- Efficacy is variable
- Memory may not improve
- Costly
- Adds to "Medication Burden" thus increasing risk for nonadherence

Memantine

- Memantine–NMDA receptor antagonist
  - Improvement in patients with moderate to severe AD and possible benefits in VaD
  - Recent phase III trials (AD) indicate significant improvement compared with placebo
  - Patients with moderately severe and severe AD benefited the most
  - Clinical trial: memantine+donepezil was positive

Memantine Studies: Moderate to Severe AD

- Reisberg et al: NEJM, 2003;348:14
  - N181 completed study duration 28 weeks
    - ADCS-ADL*: P 0.02, CIBIC* 0.06, SIB: P 0.001
    - NPI, MMSE, GDS (P value > 0.06
- Van Dyck et al: AD Assoc Disorders2007;21:2
  - N350 in a 24 week trial
  - SIB, ADCS-ADL, CIBIC-Plus,NPI showed no benefit at week 24.
- "In conclusion, this efficacy and safety study of memantine monotherapy for patients with moderate-to- severe AD did not demonstrate statistically significant treatment benefit at study end point on any primary or secondary outcome measure."

Memantine Treatment in Patients with Moderate to Severe Alzheimer's Disease Receiving Donepezil

randomized, double-blind, placebo controlled
N=404 24 weeks

- SIB P< .001
- ADCS-ADL19 p=0.03
- CIBIC-Plus p= 0.03
- NPI p= 0.01
- Mean dose of donepezil 9.25 and 9.49 mg/d
- Side effects reported: 78% memantine vs 72% P

PN Tariot, MR Farlow, GT Grossberg, S McDonald, I Gergel for the Memantine Study Group. JAMA 2004;291:317

Memantine for AD

- Improvement in patients with moderate to severe AD and possible benefits in VaD[1-2]
- Patients with moderately severe and severe AD benefited the most[1-2]
- Evidence for Efficacy in Mild AD is Lacking
- Clinical trial: memantine + donepezil was positive[1]
- Clinical trial: memantine + rivastigmine was positive[2]

VaD=vascular dementia.

1. Tariot PN et al. *JAMA*. 2004;291:317-324. **2.** Dantoine T et al. *Int. J Clin Pract*. 2006;60:110-118.

Memantine Dosing

- Week #1
  - Start memantine 5 mg po each morning
- Week #2
  - Increase dose to 5 mg po AM and PM
- Week #3
  - Increase dose to 10 mg AM and 5 mg PM
- Week #4
  - Increase dose to 10 mg AM and 10 mg PM
- Week #5
  - Maintain dose at 10 mg AM and 10 mg PM

po=by mouth.

Memantine Dosing in Patients With Renal Impairment

- Estimated creatinine clearance 5 to 29 mL/minute
- Target dose of 5 mg po twice daily
- Ebixa (memantine) in Europe is Dosed Once daily *
- *http://www.ebixa.com/prescribing_information/

Memantine Drug Interactions

- Carbonic anhydrase inhibitors
  - Alkalinization of urine (decreased clearance)
  - Change in diet (vegetarian) may also increase urinary pH
  - Alkalinizing agents, such as sodium bicarbonate
  - Ascorbic acid may acidify the urine, increasing excretion

Memantine Treatment in Patients with Moderate to Severe Alzheimer's Disease Already Receiving Donepezil

randomized, double-blind, placebo controlled
N=404 24 weeks

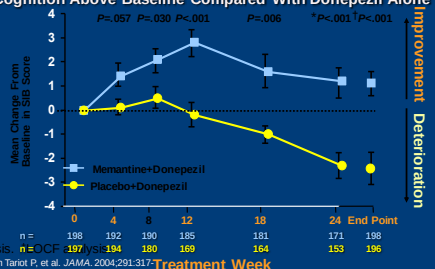
- SIB P< .001
- ADCS-ADL$_{19}$ p=.03
- CIBIC-Plus p= .03
- NPI p= .01
- Mean dose of donepezil 9.25 and 9.49 mg/d
- Side effects reported: 78% memantine vs 72% P

PN Tariot, MR Farlow, GT Grossberg, S McDonald, I Gergel for the Memantine Study Group. JAMA 2004;291:317

Memantine + Donepezil in Moderate to Severe AD Study

Results: Cognition—SIB

Memantine + Donepezil Produced Sustained Improvement in Cognition Above Baseline Compared With Donepezil Alone



Adapted from Tariot P, et al. *JAMA*. 2004;291:317-324.
Data on file, Forest Laboratories, Inc.

Medical Foods

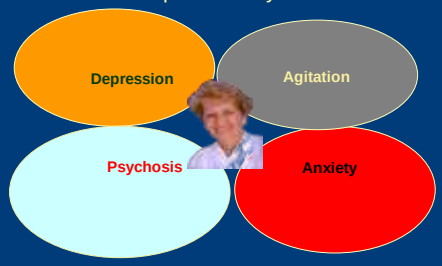
- Axona

Brief Thoughts

Managing Psychiatric Behavioral issues related to Alzheimer's disease and other dementia.

Patterns of Behavioral Disturbance

Metaphors or Syndromes



Step #1

- Document and evaluate behavior
- Is behavior precipitated by an event?
- Determine if behavior poses a hazard
- Assess behavior for possible non drug Tx
- Is behavior amenable to drug therapy?
- Determine pros and cons of drug Tx
- Select least hazardous drug
- Set goals and monitoring guidelines and date to review need for continued drug therapy.

Step #2

- Repeat Step #1

Drugs used to Treat Behavior*

- Cholinesterase Inhibitors
- Antipsychotics (typical and atypical)
- Benzodiazepines (anxiolytics)
- Anti-seizure (Mood Stabilizers)
- Antidepressants
- Beta Blockers
- Hormonal
- Psychostimulants
- Trazodone

*** No Medications are FDA approved for the treatment of psychiatric behavioral conditions associated with a dementia.**

Antipsychotic Drugs

- Typical Antipsychotic
  - A. chlorpromazine
  - B. thioridazine
  - C. loxapine
  - D. perphenazine
  - E. fluphenazine
  - F. haloperidol

  And Others.

Atypical Antipsychotics

A. clozapine
B. risperidone
C. olanzapine
D. quetiapine
E. ziprasidone
D. aripiprazole
E. paliperidone
F. lloperidone
G. asenapine

Olanzapine (Zyprexa): increased incidence of cerebrovascular events in dementia trials.

- Olanzapine: 1.3% (15/1178)
- Placebo: 0.4% (2/478

CMAJ. April 27, 2004; 170 (9)

Risperidone (Risperdal): increased rate of cerebrovascular events in dementia trials

Risperidone: 4% (29/764)

Placebo: 2% (7/466)

CMAJ. November 6, 2002; 167:11

Antidepressants

- Monoamine oxidase inhibitors
- phenelzine,tranylcypromine,selegiline(*Emsam®)
- Tricyclics
- amitriptyline, nortriptyline, imipramine, desipramine, trimipramine, doxepin, clomipramine, protriptyline
- Tetracyclics
- maprotiline, amoxapine

- *selegiline (Emsam®) transdermal patch

Antidepressants

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- Tetracyclics
- maprotiline, amoxapine

- *selegiline (Emsam®) transdermal patch

Antidepressants

- SSRI's: fluoxetine*, paroxetine*, sertraline, citalopram, escitalopram
- Bupropion
- Mirtazepine
- SNRI's: Venlafaxine, Desvenlafaxine Duloxetine, Milnacipran
- Trazodone, Nefazodone, Vilazodone)

*Generally not optimal choice

Paroxetine and Fluoxetine

- Acetaminophen with codeine
- Aripiprazole
- Risperidone
- Nortriptyline
- Metoprolol
- NSAIDS
- Tamoxifen
- Warfarin (?)

References:http://www.fda.gov/CDER/drug/drugReactions/testQuestions.htm
The Top 100 Drug Interactions, 2008 Edition; Hansten and Horn. H&H publications, Freeland WA
http://www.hanstenandhorn.com/books
Drug Interactions. LexiComp.com

SSRI's for Behavior in AD

- Effect of a Serotonin Reuptake Inhibitor on Irritability, Apathy, and Psychotic Symptoms in Patients With Alzheimer's Disease
  - ***"Conclusions:*** The use of citalopram was associated with greatly reduced irritability with- out sedation in a group of behaviorally disturbed patients with AD."
  - Haroon Siddique et al. *J Clin Psychiatry 2009;70(6):915–918*

SSRI's for Behavior in AD

- **A Double-Blind Comparison of Citalopram and Risperidone for the Treatment of Behavioral and Psychotic Symptoms Associated With Dementia**
- **Conclusion:** No statistical difference was found in the efficacy of citalopram and risperidone for the treatment of either agitation or psychotic symptoms in patients with dementia. These findings need to be replicated before citalopram or other serotonergic antidepressants can be recommended as alter- natives to antipsychotics for the treatment of agitation or psychotic symptoms associated with dementia.
- Pollock B et al. Am J Geriatr Psychiatry 15:11, November 2007

SSRI's for Behavior in AD

- Comparison of Citalopram, Perphenazine, and Placebo for the Acute Treatment of Psychosis and Behavioral Disturbances in Hospitalized, Demented Patients
- Conclusions: Citalopram was found to be more efficacious than placebo in the short-term hospital treatment of psychotic symptoms and behavioral disturbances in nondepressed, demented patients.

Bruce G. Pollock,et al.Am J Psychiatry 2002; 159:460–465.

Valproate (VA) in Dementia

- Cochrane Review: December 2010
- The new meta-analysis of pooled results showed no improvement of agitation among valproate treated patients, compared with controls, and showed an increase in adverse events (falls, infection, gastrointestinal disorders) among valproate treated patients.
- **Authors' conclusions:**
- The updated review corroborates the earlier findings that valproate preparations are ineffective in treating agitation among demented patients, and that valproate therapy is associated with an unacceptable rate of adverse effects. More research on the use of valproate preparations for agitation of people with dementia is needed. On the basis of current evidence, valproate therapy cannot be recommended for management of agitation in dementia.
- **Plain language summary: No evidence of efficacy of valproate preparations for treatment of agitation in people with dementia**

Benzodiazepines

- Antianxiety
- Antispasmodic
- Anti Seizure Activity
- Sedative/hypnotic

Equivalent Doses of BDZ's

- Lorazepam 1 mg =
  5 to 10 mg of Diazepam =
  Alprazolam 1 mg =
  Clonazepam 0.5 mg=
  Oxazepam 10 mg =
  Chlordiazapoxide 25 mg
- (http://www.benzo.org.uk/manual/bzcha01.htm)
- (Psychotropic Drug Handbook,Lippincott)

BDZ Side Effects to Watch For

- Impaired Psychomotor Skills
- Impaired Memory
- Falls
- Withdrawal Symptoms
- Additive CNS depressant to ETOH, etc.

Other Anxiolytic Medications

- Buspirone (Buspar®)
- Barbiturates (phenobarbital,butalbital)
- Meprobamate (Miltown© Equanil®)
- ETOH

Behavior

- Non Drug
- Non Drug
- Trazodone (Sleep)
- Antipsychotics
- Antidepressants
- Mood Stabilizers
- Benzodiazepines

Summary: Something to keep in mind

Who are *you*?

The Caterpillar and Alice looked at each other for some time in silence: at last the Caterpillar took the hookah out of its mouth, and addressed her in a languid, sleepy voice. 'Who are *you*?' said the Caterpillar. This was not an encouraging opening for a conversation. Alice replied, rather shyly, 'I — I hardly know, sir, just at present — at least I know who I was when I got up this morning, but I think I must have been changed several times since then.' 'What do you mean by that?' said the Caterpillar sternly. 'Explain yourself!' **'I can't explain myself, I'm afraid, sir' said Alice, 'because I'm not myself, you see**

Ch. 5 - Advice from a Caterpillar, Alice in Wonderland, L.Carroll

Quote

- Where are you going?
- How will you get there?
- How do you know when you have arrived?

Questions?

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(additional references available upon request)

k. Hamanishi

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