

Toward a Methodology for
Integrative treatment planning
focus on depression

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Part I

Foundations of methodology for
clinical integrative management

Background issues

- Methodologies in medicine reflect ways of knowing about health and illness that are a priori regarded as valid
- Beliefs about efficacy and safety of treatments are *implicit* in methodologies
- Clinical approaches used in disparate systems of medicine *are not and cannot* be validated using objective empirical means alone

In other words...

- Many systems of medicine do not use or require “objective methods” to demonstrate the existence of a putative mechanism of action or verify claimed outcomes because *the truth of a claim that a mechanism of action is present or that an outcome takes place is implicit within the conceptual framework that embodies the system of medicine.*

Philosophical Issues

- *Truth claims* of some non-conventional modalities *have not been* verified by contemporary Western science (eg, Acupuncture, “energy medicine”)
- The same is also true of some conventional treatments in widespread use (eg, Bupropion, anti-seizure medications for Bipolar Disorder)

Philosophical Issues

- Beliefs about the effectiveness of treatments in medicine have as much to do with *professional consensus* and *economic factors* as with rigorous “objective” methods for assessing empirical evidence (Kuhn, *Structure of Scientific Revolutions*).

Consequences

- These philosophical and ideological issues must be taken into account when developing a methodology for constructing practical integrative strategies combining approaches from disparate non-Western systems of medicine.

Some philosophical problems

- Establishing an ontology of phenomena associated with illness or health and a corresponding typology of *legitimate* medical practices (ie, for which **verifiable truth claims** can be made).
- Establishing standards of evidence for verifying claims of a putative mechanism of action or a reported outcome.
- Establishing a framework for a “hierarchy of evidence” for comparing disparate modalities on the basis of objective and subjective criteria.

Methodology—general goals

- Planning integrative strategies involves making clinical decisions on the basis of the “highest level” of both quantitative and qualitative evidence, keeping in mind patient preferences, values, available medical resources, and other constraints.

Kinds of modalities

- Conventional and non-conventional modalities fall into three general classes:
 - *empirically-derived*—relies on empirical test of truth claims
 - *consensus-based*—relies on shared professional agreement about mechanism or outcomes
 - *intuitive*—shared agreement and not susceptible to empirical validation.

Evolution of medicine

- Novel empirically derived, consensus-based and intuitive methods will continue to emerge
- Certain consensus-based methods will become validated, others refuted
- Certain intuitive methods will become validated, others refuted

Verifying outcomes—*not* mechanism of action

- The same methodology can be used to establish the effectiveness of any modality regardless of differences between parent systems of medicine.
- This is *true* because effectiveness is determined on basis of (*subjective or objective*) outcomes *only*—ie, there is no epistemological requirement of a *proof* of a postulated mechanism of action.

Problems inherent in *measuring* symptoms and outcomes

- Mental and emotional complaints are intrinsically subjective
- Diagnostic criteria continue to change
- Limitations of study designs
- High placebo response rates of most psychiatric disorders to conventional treatments are consistently high

Rigor and Relevance

- Because of unreliability of quantitative methods for comparing outcomes, *measures of rigor and relevance can be used* (Richardson 2002).
- “*Rigor*” is *strength of evidence* used to establish claims that a specified modality actually works—ie, outcomes claims are true.
- “*Relevance*” is *appropriateness of a specified modality* viz needs and preferences of a particular patient.

Rigor and Relevance

- In integrative medicine the clinician's goal is to find a “balance” between rigor and relevance that adequately addresses the presenting complaint, is realistic, and is acceptable to the patient.

Combining modalities

- After an acceptable balance of rigor and relevance has been achieved the problem of **compatibility** between disparate modalities is addressed.
- *Incompatible* modalities are contra-indicated in combination, while treatments that are *neutral*, *additive* or *synergistic* are compatible and desirable in combination.
- The next methodological problem is determining whether treatments are used or parallel versus sequentially

Planning integrative treatment

- A specific integrative plan is selected after quantitative and qualitative approaches have been used to determine rigor, compatibility, and mode (ie, parallel vs sequential) of implementation.
- After viable choices have been identified, the clinician and patient work together to decide on the suitability or relevance of a particular combination of modalities with respect to the specific symptoms, preferences and circumstances of the unique patient.

The integrative clinician must address five basic issues:

- Identifying the symptom pattern that is the focus of clinical attention
- Clarifying the patient's history of response to previous treatments for similar complaint
- Determining specific treatment approaches to consider
- Considering practical issues of cost, availability, patient preferences and values that determine the “shape” of a realistic and acceptable integrative strategy
- Establishing criteria for assessing outcomes

Questions to ask when planning integrative treatment

- Can the clinician identify treatments that enhance outcomes and shorten response times?
- Can the clinician identify assessment approaches that enhance the accuracy or predictive power of findings?
- Will combining the specified assessment or treatment approaches optimize assessment accuracy or treatment outcomes?
- How can (*can?*) two or more specified treatments be combined to ensure the highest degree of compatibility or synergy?

Questions to ask (cont'd)

- What are reasonable criteria for determining when considering **combining treatment modalities in parallel or sequentially** when addressing one core symptom?
- What are reasonable criteria for determining when it is appropriate to combine specified treatment modalities when addressing **complex symptom patterns**?
- What are reasonable criteria for combining specified treatments to **improve compliance or enhance patient satisfaction** with on-going care?
- What is a **practical method for measuring outcomes**—ie, for obtaining clinically useful information about outcomes?

Evidence-based medicine (EBM)

- EBM uses a “hierarchy of evidence” model to assess the significance of findings viz parameters of a study design.
- EBM relies heavily on systematic reviews and meta-analyses of conventional medical research literature to “guide the judicious use of current best evidence in making decisions about the care of individual patients (Sacket 1996).
- EBM derives clinical decisions on a case-by-case basis following a review of “best evidence” in the context of the physician’s expertise and the patient’s preferences.

Limitations of EBM

- EBM brings a new level of rigor to the analysis of diverse findings and is a potentially valuable tool in clinical treatment planning...*however*...
- Most biomedical treatments in current use do not adhere to the highest standards of EBM (Dalen 1998).
- Relatively few Western M.D.s actually practice EBM because they are not familiar with its methods or lack the time and resources to do so.
- Most conventionally trained M.D.s make treatment recommendations on the basis of their own clinical experience and intuitions, and sometimes defer to the opinions of local experts.

EBM—limitations

- The evidence-based Complementary and Alternative Medicine (CAM) working group was created to find ways to apply the rigorous methods of EBM to the evaluation of putative mechanisms of action and effectiveness of non-conventional modalities...*however...*
- Methods in EBM exclude potentially relevant research and clinical information and use a hierarchy of evidence that is biased in favor of study designs traditionally used in Western biomedical research.

EBM—limitations

- EBM assumes that clinically useful information can only be obtained from study designs using statistical measures of significance that describe directly observable “outcomes” that can be *isolated* from all other possible interfering or *confounding* variables.
- EBM assumes that if a treatment is legitimate a discrete mechanism of action has been identified or is at least “identifiable,” and that a predictable, deterministic causal relationship exists between treatment effects, the putative mechanism of action, and statistical measures of “outcomes.”
- EBM equates postulated “causes” and “effects” with discrete biological mechanisms.

EBM—limitations

- EBM does *not acknowledge* the relevance of emerging paradigms in health and illness (Richardson 2002).
- EBM asserts that study findings are “rigorous” only after sequential series of “significant” outcomes have been obtained from identical study designs using identical statistical methods.
- EBM assumes that averaged results of systematic reviews or meta-analyses of several studies can be validly applied to individuals, providing clinically pertinent guidance in treatment planning (Churchill 1999).

EBM has *implicit* biases against non-conventional approaches

- EBM assumptions about valid methods for obtaining medical information contain implicit biases against non-conventional systems of medicine (Vickers 1999).
- A consequence is that non-conventional modalities are ranked at the lowest “level” of the evidence hierarchy and many non-conventional modalities are dismissed as spurious choices before the “evidence” is objectively appraised.

Optimizing EBM

Utilizing both quantitative and
qualitative information

Quantitative criteria used to assess evidence

- Numbers of studies done, kinds of studies (basic research and clinical investigations, randomized controlled trials, cohort studies, case series, etc.) and significance of findings
- Systematic reviews or narrative reviews and significance of findings
- Studies in progress, objectives and (any) preliminary findings
- Specificity of findings by major mental or emotional symptom (ie, how does the specified diagnostic or treatment modality enhance diagnostic accuracy or improve treatment outcomes?)

Qualitative criteria used to assess evidence

- Unresolved research issues influencing study design
- Other resolved issues including safety, availability, cost, insurance coverage, etc.
- Described uses of specified modality in conjunction with other conventional or non-conventional modalities with respect to a specified mental or emotional symptom
- Best resources for additional clinical information for patients or clinicians
- Patient preferences and attitudes toward recommended modality

Kinds of evidence for developing evidence hierarchies

- Efficacy is verified and putative mechanism of action is verified
- Efficacy is verified and mechanism of action is not verified
- Efficacy is verified and putative mechanism of action is refuted
- Efficacy is refuted and putative mechanism of action also refuted
- Efficacy is verified and putative mechanism of action is unverifiable
- Efficacy is unverified and putative mechanism of action is unverifiable
- Efficacy is refuted and putative mechanism of action is unverifiable

Levels of evidence

- “N of 1” trials or systematic reviews of RCTs
- RCTs where follow-up is greater than 80%
- Cohort studies
- Case control studies or observational studies
- Expert opinion

Combined quantitative/qualitative evidence

- Four general “levels” of evidence are based on possible combinations of different kinds of quantitative and qualitative evidence supporting the use of a particular treatment modality with respect to a specified symptom pattern.
- In some cases high quality studies have been conducted but not yet analyzed in a systematic review.
- In other cases, studies may be on-going or recently concluded but not yet published, or published in specialty journals but not yet subjected to a critical peer-review process.

Combining Quantitative and Qualitative Evidence

- The combined quantitative-qualitative model provides a balanced method for weighing the evidence supporting uses of both conventional and non-conventional treatment approaches when different levels and kinds of evidence are available for disparate approaches that are being considered for possible inclusion in an integrative management plan.

Combining quantitative and qualitative evidence when planning integrative management

4 levels

Substantiated—IN CURRENT USE AND EFFECTIVE

- Systematic review findings strongly support claims that the treatment results in consistent positive outcomes for a specified symptom
- *OR* three or more rigorously conducted double-blind randomized controlled trials support claims of outcomes of the modality for a specified symptom
- *AND* the modality is in current use for the treatment of a specified symptom
- *AND* the use of the modality for a specified symptom is endorsed by a relevant professional association.

Provisional—in current use and *probably* effective

- Systematic review findings are positive but *not* compelling, or have not been conducted because of insufficient numbers of studies or uneven quality of completed studies
- *OR* three or more rigorously conducted double-blind randomized controlled trials yield positive but not compelling findings
- *AND* the modality is in current use for the treatment of a specified symptom pattern
- *AND* the use of the modality with respect to a specified symptom pattern *may* be endorsed by a relevant professional association.

Possibly effective—in current use and *possibly effective*

- Fewer than three studies or poorly designed studies have been done to determine whether a particular modality results in consistent positive outcomes with respect to a specified symptom.
- *AND* research findings or anecdotal reports are *limited or inconsistent*
- *AND* there are insufficient quality studies on which to base a systematic review or meta-analysis
- *AND* the modality is in current use but remains controversial
- *AND may be endorsed* by a relevant professional association.

***Refuted*—may be in current use but refuted by evidence**

- For a particular treatment modality findings of three or more rigorously conducted studies or at least one systematic review consistently show that the modality does not result in beneficial outcomes with respect to a specified symptom
- *OR* the conclusions of one or more systematic reviews or meta-analyses refute claims made for the treatment modality with respect to a specified symptom.
- *AND* usually not in current use or use is highly controversial
- *AND not endorsed* by a relevant professional society

Planning integrative management

*Sequential versus parallel
strategies*

Sequential versus parallel interventions (I)

- When the evidence suggests that two or more disparate treatments have equivalent efficacy, the selection of a treatment or treatments, and the order in which treatments are recommended should be determined on the basis of the following criteria:
- A treatment that was effective and well tolerated when previously used by the patient for similar symptoms should be strongly recommended.
- A treatment that was previously effective for similar symptoms but was not well tolerated should be recommended following a trial on a treatment that probably has equivalent effectiveness but may be better tolerated.

Sequential versus parallel interventions (II)

- When a treatment is probably effective for a specified symptom but requires a highly trained practitioner to administer, the approach should be recommended only when a qualified local practitioner is available, and the approach is both affordable and acceptable to the patient.
- When two or more treatments have equal effectiveness and there is similar risk of adverse effects, cost should be a determining criteria.

Sequential versus parallel interventions (III)

- When all substantiated treatments that are affordable, available and acceptable (ie, to the patient) have been tried without benefit, it is reasonable to consider provisional approaches.
- Criteria for determining the order of precedence of provisional approaches are the same as those used for substantiated approaches.
- Depending on the evidence, patient preferences, cost, and availability of qualified practitioners, combining a provisional approach with a substantiated approach may provide synergistic benefits.

Sequential versus parallel interventions (IV)

- As new approaches are tried, previously tried approaches should be discontinued unless there is evidence that they are beneficial or may have synergistic effects when used with the new approach.
- Possibly effective treatments should be considered only after substantiated or provisional approaches (ie for the specified symptom) have been tried without benefit or in cases where evidence supports the use of a possibly effective approach together with a substantiated or provisional approach.

Sequential versus parallel interventions (V)

- In cases where all substantiated and provisional approaches have been tried without benefit, or are unavailable, unaffordable or unacceptable to the patient, it is reasonable to try a *possibly effective* approach if there is a qualified local practitioner and the patient is motivated to try that approach.
- In such cases, the *N=1 method* can be used to evaluate a particular treatment for a specific patient even in the absence of compelling evidence.
- Using the N=1 approach will help the clinician to determine whether a *possibly effective* treatment is potentially beneficial for the patient and will lead to an appropriate individualized treatment plan.

Part II

The integrative management of
depressed mood

Case vignette

- 57 year old retired stock broker
- Recovering alcoholic with 11 yrs sobriety
- Elevated cholesterol on statin
- First MDE age 18: fatigue, hopelessness, hypersomnolence, frequent SI (resolved without Rx after 3 months)
- Subsequent MDEs approx. every 3 to 5 years: vegetative sx, frequent SI

Treatment Hx

- First treated age 30 Prozac 20mg with significant improvement but discontinued p. 1 yr due to sexual AEs and weight gain
- Recurring MDE 3 yrs later Zoloft 150mg, worsened, SI, hospitalized: LiCO₃ augmentation with significant improvement
- Discontinued Lithium after 3 months: tremor, weight gain, nausea.

Treatment Hx

- Subsequent therapeutic trials on Paxil, Serzone, Celexa, Lexapro, Effexor, with *initial* positive results
- Now on Remeron 15mg “munchies” and weight gain
- “They work for a while...then peter out”
- No previous CAM or integrative Rx
- Retired last year and moved to suburbs
- Found integrative clinic and “open” to new approaches

Integrative Rx—Assessment and Formulation

- M.D./L.Ac. Does conventional assessment and Chinese medical assessment
- Med-psych, social and spiritual hx incl. detailed hx of previous conventional and CAM Rx
- Conventional Dx is MDE, recurrent, now with **moderate depressed mood, consider depressed mood due to low cholesterol**
- Chinese Dx (pulses, tongue) ascribes mood sx to **stagnant liver qi**
- Labs: serum total cholesterol and triglycerides, RBC folate level, and thyroid studies

Integrative treatment planning

- Review of substantiated non-conventional approaches for moderate depressed mood including life style changes, acupuncture, and other therapies that improve **moderate depressed mood** when used alone or in combination with conventional antidepressants.

Treatment planning—patient preferences

- Patient skeptical about Chinese medicine which is not pursued
- Patient has strong interest in supplements and exercise
- Both approaches are beneficial for moderate depressed mood
- Both are available options, affordable and realistic for patient

Treatment—initial integrative recommendations

- *Initial plan:* continue current dose of mirtazepine (15mg), start trial on adjunctive SAME with gradual taper to 400mg BID, vitamin supplements (B-12, folate), daily aerobic exercise, improved diet and regular stress management.
- Document informed consent of SAME trial p. reviewing AE risks

3 week follow-up

- “nothing is working...going downhill fast...”
- Still craving sweets, “sad” all the time, demoralized and not exercising
- RBC folate low-normal, serum total cholesterol 155mg/dl (low NL). Thyroid studies WNL.
- No change in Liver qi stagnation
- Takes B vitamins, SAME 200mg/am only (inferior brand)
- Working in garden, listening to music

Modified plan

- Change to quality brand of SAME and continue with initial titration schedule to 400mg BID
- Encourage daily work in garden and aerobic workouts if motivated
- Encourage listening to music for stress
- Review option of tapering/DC Remeron if significant response to SAME

2 week follow-up

- Significantly “brighter”
- Exercising almost daily
- SAME 400mg BID with mild GI distress
- “munchies” still a problem
- Family practice MD reduced statin dose, repeat total serum cholesterol now 180 (protective HDL/LDL ratio)

One month follow-up

- Mood still improved
- Gradual weight loss
- Sustained exercise program
- Good compliance with SAME, minimal AEs
- Night-time craving sweets continues
- **New Rx recommendation:** hold Remeron pending continued euthymic mood while on maintenance SAME with B-vitamins

On-going care

- Regular 4-6 week FU X 6 months then quarterly pending euthymic on present regimen
- Follow serum cholesterol q 6 months adjust statin PRN (DC pending cont'd weight loss)
- Serial energetic assessment (pulse dx)
- Maintenance SAME on-going (MDE recurrent)
- Encourage continued exercise, healthy diet and life-style changes
- Consider supportive psychotherapy