AAPT Approach to Creating a Disease Taxonomy

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Diagnostic Criteria

- Criteria lead to clear dichotomous diagnostic decision
- Mutually exclusive criteria for confusable conditions
- When followed as worded, criteria lead to same diagnosis by different clinicians

DSM5 Criteria: Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (**Note:** In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (**Note:** In children, consider failure to make expected weight gain.)

…….. [List of 9 Symptoms]

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or another medical condition.

Example AAPT Criteria

Table 1. Diagnostic Criteria for Chronic Central Neuropathic Pain Associated With SCI

1. Diagnostic test confirming SCI
2. Continuous or recurrent pain after an SCI, with onset of pain at the time of SCI or up to 1 year after SCI. Any later onset should prompt examination of other causes such as the development of syringomyelia
3. Pain duration of at least 3 months
4. Pain is described within the area of the body affected by the SCI*
5. Pain is associated with sensory changes in the same neuroanatomically plausible distribution, as indicated by the presence of at least 1 positive sensory sign (eg, dynamic mechanical or cold allodynia) or 1 negative sensory sign (eg, elevated thresholds to cold or warm or decreased sensation to touch, pinprick, or thermal stimuli)
6. There is no other diagnosis that better explains the pain

Widerstrom-Noga et al., 2017

Two Key Conceptual Issues

- Validity
- Reliability
  - Necessary but not sufficient for criteria to be valid
  - Could have totally reliable criteria that are not at all valid

Types of Reliability

- Inter-Rater Reliability
  - Would 2 clinicians agree on presence/absence of specific criteria?
  - Would 2 clinicians agree on diagnostic decisions made using the full set of diagnostic criteria?
- Test-Retest Reliability
  - Are diagnostic decisions stable over time?
    - Within same clinician = “Intra-Rater Reliability”
    - Across multiple clinicians

Reliability

- Reliability of individual signs and symptoms comprising the criteria

- Are they operationalized well?
  - Example from 1994 CRPS criteria: "*evidence of changes in skin blood flow*…" – How indexed?
  - Hypothetical example: "*Progressive distal sensory abnormalities…*" – Positive? Negative? Painful?

Reliability

- Reliability of decision rules in the criteria

- Example:
  - *Decision rule requiring that 3 of 5 criteria be met*

    VERSUS
  - *Decision rule in which criterion A must be met, at least 2 of 5 symptoms for Criterion B must be present, and that Criterion C must be met only if less than 4 symptoms in criterion B are present*

Reliability

- Context of test-retest reliability is important:
  - Would clinical features or diagnostic decisions be expected to be stable over the time period evaluated?

- Criteria that cannot lead to the same diagnostic decision within and between providers over brief periods of time are likely to be of little use clinically

Reliability Study Designs

- Can focus on individual diagnostic criteria or overall diagnostic decisions
- Vignette studies
  - Written descriptions or videotaped evaluations
  - Best for initial fine-tuning of wording?
- Field trials
  - In-person evaluation by multiple clinicians of the same patients

Reliability Measures

- Measures of agreement over time and/or between raters *correcting for chance*
  - Kappa (ƙ)
    - Dichotomous variables only
  - Intraclass correlation coefficient (ICC)
    - Ordinal, interval, and ratio variables
  - Range = 0 – 1.0 (higher = greater reliability)
  - Values >0.60 generally considered adequate

Diagnostic Validity

- Do criteria reflect what they are supposed to reflect?
  - If a patient gets the diagnosis, does she really have that condition?

- Leads to thorny conceptual issue…….

Diagnostic Validity

- What is “X Pain Syndrome”?
  - What defines it?
  - Who defines it?
  - How do we measure it?
  - Do you just “know it when you see it?”
  - Does everyone agree on this?

Diagnostic Validity Issues

- Pain is inherently subjective
- Definitive pathophysiology not known
- No external objective “gold standard” for evaluating diagnostic accuracy
- “Fuzzy Boundaries” between conditions

Diagnostic Validity Issues

- "Pain Syndromes" are only indirectly measurable constructs that we assume exist

- Can only show relative validity (not absolute)

Types of Construct Validity

- **Content Validity** - adequate domain coverage
- "**Internal Validity**"- internal structure of criteria
  - Subgroups of signs/symptoms appropriate?
- **Concurrent Validity** - identified "gold standard"
- **Convergent Validity** - "nomological net"
  - Correspond as expected with external measures?
  - E.G. – Elevated Temporal summation in FMS…
- **Discriminant Validity** - Distinguish groups?

What "Gold Standard" Do We Use?

- Current consensus-based diagnostic criteria
  - 2012 IASP Criteria for CRPS
- "Usual method of diagnosis"
  - 1990 ACR Fibromyalgia Criteria
- "Expert clinician diagnosis"
  - DSM III-R Psychiatric Diagnostic Criteria
- Previously published diagnostic criteria
  - DSM IV Psychiatric Diagnostic Criteria

Empirical Validation Approaches

- Statistical pattern recognition techniques
  - Principal components analysis
  - Cluster analysis
  - Latent class analysis
  - Classification and Regression Tree (CART) models

Empirical Validation Approaches

- Identify groups of statistically similar patients based on patterns of clinical features
    - ID prototypic presentation of presumed syndrome
- Identify groups of signs/symptoms that cluster together within a given patient population
    - ID individual criteria – features with common basis
- Show whether two conditions are distinct
    - Cluster example - Migraine vs. Tension type headache

Empirical Validation Approaches

- Common Validation Questions:
  - Do proposed criteria have concurrent validity relative to existing reference standard?
  - Do revised criteria improve discriminative validity relative to existing criteria?

Empirical Validation Approaches

- Measures of diagnostic accuracy
  - Sensitivity – TP rate
  - Specificity – TN rate
  - Positive and Negative Predictive Power
    - Drawback – dependent on base rate in population
  - Positive and Negative Likelihood Ratio
    - NOT dependent on base rate

Empirical Validation Approaches

- Diagnostic threshold (decision rules in criteria) influence both sensitivity and specificity
  - E.G. – 2 of 4 **vs.** 3 of 4 criteria met for diagnosis

- Receiver Operating Characteristics (ROC curve)
  - Plots sensitivity vs. specificity for all diagnostic thresholds – can identify optimal balance

Instructive Example: CRPS (1994)

1. The presence of an initiating noxious event, or a cause of immobilization. [**NOT ACTUALLY REQUIRED**]
2. Continuing pain, allodynia or hyperalgesia with which the pain is disproportionate to the inciting event.
3. Evidence at some time for edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain.
4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

Merskey & Bogduk, 1994

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Diagnostic Research Questions

- Do the criteria adequately capture the core defining signs/symptoms of CRPS?
- Is the “structure” of the criteria optimal?
  - Layout of signs/symptoms
  - Diagnostic decision rules
- Both of these influence sensitivity/specificity

Diagnostic Research Questions

- Diagnostic Sensitivity
  - How well do criteria identify CRPS+ cases?
- Diagnostic Specificity
  - How well do criteria screen out non-CRPS cases?

Content Validity of CRPS Criteria

- Historical literature reveals variety of “key” signs and symptoms

- 1994 IASP criteria DO include:
  - Allodynia and Hyperalgesia
  - Skin Temperature/Color Changes
  - Sweating Changes
  - Edema

Content Validity of CRPS Criteria

- 1994 IASP criteria DO NOT include:
  - Hair/Nail/Skin Changes
  - Tremors
  - Dystonia
  - Diminished active range of motion
  - Hemi-Body Hypoesthesia
  - CNS Abnormalities (brain imaging)
  - Osteoporosis (bone scan and radiograph)
  - Diminished pain with SNS block

CRPS DATABASE FORM

PATIENT ID: _____ **EXAM DATE:** ____/____/____ **STUDY SITE:** _____

DIAGNOSIS: ☐**CRPS-I** ☐**CRPS-II** (☐**Y** ☐**N Confirmed by EMG/NCV?**) ☐**Non-CRPS**:_____

ETIOLOGY: ☐ Crush ☐ Surgery ☐ Fracture ☐ Laceration ☐ Other: _____

DATE INJURY: ____/____/____ DATE SX ONSET:____/____/____ LOCATION: ☐ L ☐ R ☐ UE ☐ LE

SPREADING: ☐None (distal only) ☐Proximal Limb ☐Mirror Image ☐Hemilateral ☐All 4 Quadrants

SYMPTOMS (as reported by patient now or previously):

Circle "Yes" or "No" for each. *Comments*:

YES NO Initiating noxious event or immobilization _____

YES NO Continuing, disproportionate pain _____

YES NO Hyperesthesia. *If yes, specify*: ☐Allodynia ☐ Hyperpathia _____

YES NO Hypoesthesia. *If yes, specify location*: _____ _____

YES NO Temperature asymmetry. *If yes, specify*: ☐ Cold ☐ Warm ☐ Labile _____

YES NO Color asymmetry _____

YES NO Sweating asymmetry _____

YES NO Edema _____

YES NO Dystrophic changes. *If yes, specify*: ☐ Nails ☐ Hair ☐ Skin _____

YES NO Motor abnormalities. *If yes, specify*: ☐ Weak ☐Tremor ☐ Dystonia _____

YES NO Decreased ROM _____

SIGNS (as observed by examiner this date). Note any comments on back:

YES NO Hyperalgesia to pinprick.

YES NO Hypoesthesia to light touch.

YES NO Allodynia. *If yes, specify to*: ☐ Cold ☐ Heat ☐ Light Touch ☐ Vibration ☐ Deep Joint Pressure

YES NO Asymmetric Edema: _____cm^3 Affected Side _____cm^3 Unaffected Side

YES NO Sweating asymmetry. *If yes, specify*: ☐ **Increased** on Affected Side ☐ **Decreased** on Affected Side

YES NO Temperature asymmetry by palpation. *If yes, specify*: ☐ Affected Side **Cooler** ☐ Affected Side **Warmer**

YES NO Color asymmetry. *If yes, specify*: Affected side: ☐ Red ☐ Blue/Pale ☐ Mottled ☐ Scar

YES NO Dystrophic changes. *If yes, specify*: ☐ Nails ☐ Hair ☐ Skin (shiny,thin) Notes:_____

YES NO Motor abnormalities. *If yes, specify*: ☐ Weakness ☐ Tremor ☐ Dystonia

YES NO Decreased Active ROM.

YES NO Reflexes in affected area. *If yes, specify*: _____

** *Evaluate light touch sensitivity.* Specify:

Face: **Affect Side**: ☐Hypoesth ☐Normal ☐Allodyn **Unaff Side**: ☐Hypoesth ☐Normal ☐Allodyn

Chest: **Affect Side**: ☐Hypoesth ☐Normal ☐Allodyn **Unaff Side**: ☐Hypoesth ☐Normal ☐Allodyn

Bicep: **Affect Side**: ☐Hypoesth ☐Normal ☐Allodyn **Unaff Side**: ☐Hypoesth ☐Normal ☐Allodyn

Thigh: **Affect Side**: ☐Hypoesth ☐Normal ☐Allodyn **Unaff Side**: ☐Hypoesth ☐Normal ☐Allodyn

***Evaluate palmar/navicular temperature by IR thermometry.* Specify: **Affected**:_____ °C **Unaffected**:_____ °C

***Evaluate Active ROM.* Specify:

Elbow/Knee: **Affect Flex**:____ ° **Affect Ext**:____ ° **Unaff Flex**:____ ° **Unaff Ext**: ____°

Wrist/Ankle: **Affect Flex**:____ ° **Affect Ext**:____ ° **Unaff Flex**:____ ° **Unaff Ext**: ____°

Study of Internal Validity

- Multi-site study
- n = 123 patients meeting 1994 IASP criteria for CRPS
- All patients underwent standardized evaluation of CRPS signs and symptoms using structured database form

Harden et al., 1999

Internal Validity

- Does it make sense to include both objective signs and subjective symptoms?

Internal Validity

Characteristic	Signs (%)	Symptoms (%)
Temp Asymmetry	56.3	78.7
Color Δ	66.4	86.9
Sweating Δ	24.2	52.9
Edema	56.1	79.7
Nail Δ	9.3	21.1
Skin Δ	19.5	24.4
Weakness	56.1	74.6
↓ ROM	70.3	80.3

Internal Validity

- Is the grouping of signs and symptoms in each criterion supported by the data?

IASP CRPS Criteria (1994)

1. The presence of an initiating noxious event, or a cause of immobilization (*not required*).
2. Continuing pain, allodynia or hyperalgesia with which the pain is disproportionate to the inciting event.
3. Evidence at some time for edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain. [Too Low a Threshold??]
4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

Internal Validation Study

- Principal components analysis used to identify groups of signs and symptoms with common underlying relationships

Harden et al., 1999

Internal Validation Study

- CRPS signs and symptoms group into 4 relatively independent factors:
  - **Sensory** (IASP criterion 2)
  - **Vasomotor** (IASP criterion 3)
  - **Sudomotor/Edema** (IASP criterion 3)
  - **Motor/Trophic** (*not included*)
- Absence of motor/trophic features from IASP criteria may be problematic

Internal Validation Study

- Conclusions:
  - IASP CRPS criteria are **not** internally valid
  - Combining vasomotor, sudomotor, and edema in criterion 3 may lead to poor specificity and overdiagnosis

- Suggested revision of criteria was needed

Discriminant Validity Study

- Multi-site study
- n = 117 patients meeting 1994 CRPS criteria
- n = 43 patients with non-CRPS neuropathic pain (e.g., PHN, diabetic neuropathy)

- All patients underwent standardized evaluation of CRPS signs and symptoms

Bruehl et al., 1999

Discriminant Validity Study

- 1994 CRPS vs. non-CRPS neuropathic pain
  - Diagnostic sensitivity = 0.98
  - Diagnostic specificity = 0.36
    - Implies that non-CRPS look much like 1994 CRPS features
- 1994 IASP criteria may lead to overdiagnosis

Bruehl et al., 1999

SIDE NOTE

- For CONCEPPT purposes, could use similar methods to discriminate between any two similar but distinct disorders based on proposed criteria

Improving CRPS Diagnosis?

- Require presence of objective signs in addition to self-reported symptoms
- Include motor/trophic changes in diagnosis
- List vasomotor features and edema/ sudomotor features as two separate criteria
- Proposed changes (to be evaluated) agreed upon at 2003 meeting in Budapest, Hungary

Bruehl et al, 1999; Harden et al., 1999

Budapest *Clinical* CRPS Criteria

- Continuing pain which is disproportionate to any inciting event

Budapest *Clinical* CRPS Criteria

- At least one symptom reported in 3 or more of the following categories:
  - Sensory
    - Hyperalgesia and/or allodynia
  - Vasomotor
    - Temperature asymmetry and/or skin color changes
  - Sudomotor/Edema
    - Edema and/or sweating changes/asymmetry
  - Motor/Trophic
    - Weakness, ↓ ROM, skin/nail/hair changes, tremor, dystonia

Budapest *Clinical* CRPS Criteria

- At least one sign *at time of evaluation* in 2 or more of the following categories:
  - Sensory
    - Hyperalgesia (pinprick) and/or allodynia (touch or DSP)
  - Vasomotor
    - Temperature asymmetry and/or skin color changes
  - Sudomotor/Edema
    - Edema and/or sweating changes/asymmetry
  - Motor/Trophic
    - Weakness, ↓ ROM, skin/nail/hair changes, tremor, dystonia

Budapest *Research* CRPS Criteria

- Different threshold for diagnostic signs:
  - Requires 3 or more sign categories be positive
- Intended to maximize specificity for research samples

2010 Budapest Validation Study

Diagnostic Criteria	Sensitivity	Specificity
1994 IASP	1.00	0.41
Budapest Clinical	0.99	0.68
Budapest Research	0.78	0.79

Harden et al., 2010

NEW IASP Criteria for CRPS

- IASP taxonomy committee recommended adoption of Budapest criteria as new IASP CRPS diagnostic criteria (3/11)

- Formally adopted by IASP board (1/12)

Take-Home Point

- **The exact wording of criteria and decision rules matter!!!**

- Wording changes can alter diagnostic accuracy, sometimes dramatically