UNDERSTANDING
ANXIETY

Now more than ever
we are worrying ourselves sick

What scientists have learned
The best ways to cope
Calming the Unquiet Mind: An Integrative Understanding and Treatment of Generalized Anxiety Disorder

Pratap R. Chokka, MD, FRCPC
Clinical Professor, University of Alberta
Psychiatrist, Grey Nuns Hospital
CEO, Chokka Center for Integrative Health
Edmonton, Alberta, Canada
Faculty Disclosure

- **Dr. Chokka**: Advisory Board—Janssen Pharmaceutical, Lundbeck, Pfizer, Purdue, Sunovion; Grant/Research Support—Lundbeck; Speakers Bureau—Janssen Pharmaceutical, Pfizer, Purdue, Sunovion.
Disclosure

• The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
  – The off-label use of agomelatine, aripiprazole, bromazepam, bupropion XL, buspirone, citalopram, divalproex chrono, fluoxetine, hydroxyzine, imipramine, ketamine, mirtazapine, olanzapine, pexacerfont, pregabalin, propranolol, quetiapine XR, quetiapine, risperidone, sertraline, tiagabine, trazodone, vilazodone, vortioxetine, and ziprasidone for the treatment of generalized anxiety disorder will be discussed.

• Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

• This activity has been independently reviewed for balance.
Learning Objectives

• Describe the neurobiology of generalized anxiety disorder (GAD)
• Apply evidence-based treatments to the “real world” of clinical practice
• Employ a holistic, integrative approach to combining medications, therapy, mindfulness, and other novel approaches to treat GAD
Why Do People Become Anxious?

• Prepares us for Threat
• A continuum between normal and adaptive to pathological and maladaptive
• A problem of Signal Detection
• Anxiety overlaps with Fear but is different

12-Month and Lifetime Prevalence of Anxiety Disorders in the United States

**National Comorbidity Survey Replication (NCS-R)**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>12-month prevalence</th>
<th>Lifetime prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAD</td>
<td>3.1</td>
<td>5.7</td>
</tr>
<tr>
<td>Social Anxiety Disorder</td>
<td>6.8</td>
<td>6.8</td>
</tr>
<tr>
<td>Panic</td>
<td>2.7</td>
<td>3.5</td>
</tr>
<tr>
<td>PTSD</td>
<td>4.7</td>
<td>6.7</td>
</tr>
<tr>
<td>MDD†</td>
<td>16.6</td>
<td>16.6</td>
</tr>
</tbody>
</table>

*Based on DSM-IV criteria; †MDD data provided for comparison.

GAD = generalized anxiety disorder; MDD = major depressive disorder; PTSD = posttraumatic stress disorder.

GAD: A Brief Modern History

- *DSM-I*: Psychoneurotic Disorders
- *DSM-II*: Anxiety Neurosis
- *DSM-III*: GAD (separate from panic disorder)
- *DSM-IV*: Reduction in symptoms, 6-month duration, difficult to control the worry
MY ANXIETIES HAVE ANXIETIES.
DSM-5 Diagnostic Criteria for GAD

- Excessive anxiety and worry > 6 months
- Difficult to control the anxiety
- Accompanied by at least 3 of the following symptoms:
  - Restlessness, or feeling keyed up or on edge
  - Being easily fatigued
  - Difficulty concentrating, or mind going blank
  - Irritability
  - Muscle tension
  - Sleep disturbance (difficulty falling/staying asleep, or restless, unsatisfying sleep)
- Anxiety, worry, or physical symptoms cause clinically significant distress or impairment
- Present most of the time for > 6 months
- Not due to medication, illness, or substance use

GAD: Epidemiology

- 5.7% lifetime prevalence in the NCS
- F > M 2:1
- Mean age of onset: Adolescence
- GAD symptoms often detected in childhood
- Second most common psychiatric disorder after depression in primary care
- 8% point prevalence in primary care
- Occurs in 22% of high utilizers of medical care

GAD is Underrecognized and Undertreated

<table>
<thead>
<tr>
<th>GAD is underrecognized by patients</th>
<th>➢ Patients typically have symptoms of GAD &gt; 10 years before seeking medical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAD is underrecognized by physicians</td>
<td>➢ Only 34% of patients are diagnosed correctly by a primary care physician</td>
</tr>
<tr>
<td>GAD is undertreated</td>
<td>➢ Only about 20% of patients with GAD currently are receiving treatment</td>
</tr>
<tr>
<td>Achieving remission in GAD is a challenge</td>
<td>➢ Few patients achieve complete remission</td>
</tr>
</tbody>
</table>

Linking Neurobiology of GAD to Core Psychological Processes

Genetic Influences

Fear Circuitry
- Sensory cortex
- Thalamus
- Anterior cingulate
- Amygdala
- Hippocampus
- Prefrontal cortex

Disruption in Core Psychological Processes
- Biased threat appraisal
- Enhanced fear conditioning
- Resistance to extinction

Environmental and Epigenetic Influences

Clinical Features
- Trait anxiety
- Anxiety disorder

Neurobiology of Anxiety

Cognitive Functions

Cognitive Conspiracies

Prefrontal Cortex

Thalamus

Amygdala

Hippocampus

PROCESSING

Neurotransmitter Systems in GAD

- Multiple anxiolytic pathways
- Limited findings suggest that several neurotransmitter systems may contribute to the neurobiology of anxiety disorders
  - GABAergic
  - Noradrenergic
  - Serotoninergic
  - Glutamatergic

GABA = gamma-amino butyric acid.

GAD Burden of Illness
Economic Impact of GAD: Work Productivity

- **Lost time**
  - Individuals with GAD were absent from work an average of 6.3 days/month worldwide
  - In the United States, workers with GAD averaged 4 missed work days/month

- **Lost productivity**
  - 11% reported a > 50% decrease in productivity
  - 23% reported a 10% to 49% decrease in productivity
  - 18% of individuals reported a 0% to 9% reduction in work productivity

- **Unemployment**
  - In one survey, 21.9% of primary care patients with GAD were unemployed

GAD Diminishes QOL

• Compared with healthy controls, patients with GAD were significantly more likely to report:
  – A poor sense of overall well-being
  – Dissatisfaction with job or main activity in life
  – Dissatisfaction with family life
  – An increased number of adverse events in life
• Excessive worry about minor matters
  – Impairs social functioning and close relationships
  – Creates stress among family members
• Heightened state of vigilance and arousal increases emotional reactivity in social situations

QOL = quality of life.
Chronic Exposure to the Stress Response in Untreated GAD: *Medical Consequences*

<table>
<thead>
<tr>
<th>Stress Response</th>
<th>Medical Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained HPA Activation</td>
<td>✓ Hypercortisolemia&lt;br&gt;✓ Hypocortisolemia&lt;br&gt;✓ Glucocorticoid signaling disruption either way&lt;br&gt;✓ Loss of ability to shut off HPA axis</td>
</tr>
<tr>
<td>Uncontrolled Cytokine-Mediated Inflammatory Activity and NE Release</td>
<td>✓ Hippocampal and prefrontal cortex neurodegeneration&lt;br&gt;✓ Hypertension&lt;br&gt;✓ Coronary artery disease&lt;br&gt;✓ Obesity&lt;br&gt;✓ Type 2 diabetes&lt;br&gt;✓ Hyperlipidemia/hypercholesterolemia&lt;br&gt;✓ Immune dysfunction</td>
</tr>
</tbody>
</table>

HPA = hypothalamic–pituitary–adrenal; NE = norepinephrine.
Psychiatric Comorbidities in Patients with GAD: Lifetime Adjusted Odds Ratio

Patients with GAD + Psychiatric Comorbidity*

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Lifetime Adjusted Odds Ratio and 95% CI</th>
</tr>
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<tbody>
<tr>
<td>Any Mood Disorder</td>
<td>14.1 (12.20–16.31)</td>
</tr>
<tr>
<td>Bipolar Disorder I</td>
<td>8.8 (7.43–10.48)</td>
</tr>
<tr>
<td>Social Phobia</td>
<td>8.4 (7.13–9.81)</td>
</tr>
<tr>
<td>Any Anxiety Disorder</td>
<td>7.5 (6.53–8.50)</td>
</tr>
<tr>
<td>Panic Disorder</td>
<td>7.3 (6.25–8.41)</td>
</tr>
<tr>
<td>Any Personality Disorder</td>
<td>7.2 (6.31–8.32)</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>7.1 (5.92–8.64)</td>
</tr>
<tr>
<td>MDD</td>
<td>5.7 (5.00–6.50)</td>
</tr>
<tr>
<td>Bipolar Disorder II</td>
<td>5.0 (3.54–7.03)</td>
</tr>
<tr>
<td>Any Drug Use Disorder</td>
<td>2.7 (2.35–3.17)</td>
</tr>
<tr>
<td>Any Alcohol Use Disorder</td>
<td>2.2 (1.89–2.51)</td>
</tr>
</tbody>
</table>

GAD Often Precedes MDD and May Increase the Risk for Developing MDD

- Often precedes MDD
- Increases risk for developing MDD
- Increases risk for relapse or persistence of MDD

GAD: Diagnosis

- GAD is a clinical diagnosis
- The diagnosis of GAD can be challenging
  - Recognition improves when clinicians appreciate that anxiety can underlie unexplained somatic symptoms
- Simple screening tools can assist in detecting hidden anxiety
- A patient interview will help to confirm the diagnosis

Initial Assessment

A. Identify anxiety symptoms (somatic)
B. Conduct differential diagnosis (Medical/Psych)
C. Identify specific anxiety disorder and rule out medical causes (screening tools, blood work, etc.)
D. Consider psychological and pharmacologic treatment
E. Perform follow-up

Primary Reasons for Presentation of Patients with GAD

- Somatic complaints: 47.8%
- Pain: 34.7%
- Sleep Disturbance: 32.5%
- Depression: 15.5%
- Anxiety: 13.3%

Patients with GAD rarely present because of their psychological symptoms.

Frequent Visits to Primary Care Clinic Leading to an Enlarged Chart

- Unexplained symptoms and comorbidity
- Negative anticipatory thinking
- Uncontrollable worry about ordinary day-to-day things:
  - Family, money, illness
- Frequent and multiple negative tests (cardiac, GI, etc.) suggest GAD
- NYD = Not Yet Diagnosed
  - Non-cardiac, atypical chest pain, GI

GI = gastrointestinal.
### Assessment Scales: GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems?

<table>
<thead>
<tr>
<th></th>
<th>Feeling nervous, anxious, or on edge</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Not being able to stop or control worrying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Worrying too much about different things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Trouble relaxing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Being so restless that it is hard to sit still</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>Becoming easily annoyed or irritable</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>Feeling afraid as if something awful might happen</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Total score* _____ = (Add columns) ___ + ___ + ___

### Hamilton Anxiety Rating Scale (HAM-A)

<table>
<thead>
<tr>
<th>Item</th>
<th>Psychic</th>
<th>Somatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Anxious mood</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>2 Tension</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>3 Fears</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>4 Insomnia</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>5 Intellectual (cognitive)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>6 Depressed mood</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>7 Somatic (muscular)</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>8 Somatic (sensory)</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>9 Cardiovascular symptoms</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>10 Respiratory symptoms</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>11 Gastrointestinal symptoms</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>12 Genitourinary symptoms</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>13 Autonomic symptoms</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>14 Behaviour at interview</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

**HAM-A Scoring**
- > 25: Severe anxiety
- 19–25: Moderate anxiety
- 8–18: Mild anxiety

Each item is scored from 0 (not present) to 4 (severe).

Sheehan Disability Scale (SDS)

- Measures functional outcomes across
  - Work
  - Social/leisure activities
  - Family life/home responsibilities
- Measures the level of functional impairment associated with MDD
  - 0 = no disability
  - 10 = very severe disability

Effective Treatment Improves QOL and Reduces Health-Related Burdens

Reducing symptoms and improving functionality should result in:

- Improvements in QOL
- Greater workplace productivity
- Decreased risk for depression
- Reduction in the number of psychiatric comorbidities
- Reductions in wasteful health care expenditure

GAD: Restoring Function is the Treatment Goal
Ultimate Goals of Anxiety Management Should Be...

- Eliminate symptoms of anxiety
- Eliminate phobic avoidance
- Restore ability to carry out everyday activities (work, family, recreation, etc.)

Functional Recovery

## GAD: Recommendations for Pharmacotherapy

<table>
<thead>
<tr>
<th>Category</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line</strong></td>
<td>Duloxetine, escitalopram, paroxetine, pregabalin, sertraline, venlafaxine XR, agomelatine</td>
</tr>
<tr>
<td><strong>Second-line</strong></td>
<td>Alprazolam, bromazepam, bupropion XL, buspirone, diazepam, hydroxyzine, imipramine, lorazepam, quetiapine XR, vortioxetine</td>
</tr>
<tr>
<td><strong>Third-line</strong></td>
<td>Citalopram, divalproex chrono, fluoxetine, mirtazapine, paroxetine CR, trazodone</td>
</tr>
<tr>
<td><strong>Adjunctive Therapies</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Second-line</strong></td>
<td>pregabalin</td>
</tr>
<tr>
<td><strong>Third-line</strong></td>
<td>aripiprazole, olanzapine, quetiapine, quetiapine XR, risperidone</td>
</tr>
<tr>
<td><strong>Not recommended</strong></td>
<td>ziprasidone</td>
</tr>
<tr>
<td><strong>Not Recommended</strong></td>
<td>Beta blockers (propranolol), pexacerfont, tiagabine</td>
</tr>
</tbody>
</table>

“I’m trying to develop an ‘attitude of gratitude’ but the best I can muster is a ‘sentiment of resentment’.”
Psychotherapy

• **First-line**: CBT (better than placebo and wait list)
  Internet-based or computer-based CBT effective
  Effective up to 24 weeks
  Very few studies have evaluated CBT and medications

• Metacognitive Therapy
• Acceptance Based Therapy
• Short-Term Psychodynamic Therapy

• **Adjunctive Treatment**: IPT, Motivational Interviewing, Exercise

Some Promising Treatments

• IV Ketamine
• Transcranial Magnetic Stimulation
• Silexan (lavender oil) – Level 1 Evidence
• Passiflora (passion flower) – Level 2
• Negative study with valerian
• Small adjunctive studies with resistance training and aerobic exercise
• Open studies with adjunctive meditation and yoga

Treatment for Acute Transient Anxiety

- BZDs
  - Short-term, intermittent course of anxiolytic therapy, particularly for patients with episodic anxiety

Prolonged Treatment Indicated

- SSRIs
- SNRI
- VLZD
  - Evaluate after 8 weeks of treatment

Responsive
- 6 months to 1 year of treatment for medication and booster sessions for CBT

Nonresponsive
- Reassess diagnosis
- Examine for comorbidity
- Assess for treatment adherence
- Assess for adequate dose
- Side effects intolerable

Treatment Options
- Switch to another first-line treatment
- Augmentation with CBT if on medication only or the reverse if started with CBT
- Augmentation with a BZD
- Augmentation with a second antidepressant
- Low-dose augmentation with an antipsychotic

BZD = benzodiazepine; SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin norepinephrine reuptake inhibitors; CBT = cognitive-behavioral therapy; VLZD = vilazodone.
Neurotic suffering is an unconscious fraud and has no real merit, as has real suffering.
My Clinical Observations: 
*Emerging Evidence for Managing Anxiety*

- Emotional Styles (Mindfulness, Meditation)
- Positive Psychology/Psychiatry
- Resiliency
- Relationships
THE
EMOTIONAL
LIFE OF YOUR
BRAIN

How Its Unique Patterns Affect the Way You Think,
Feel, and Live—and How You Can Change Them

RICHARD J. DAVIDSON, Ph.D.
and SHARON BEGLEY,
bestselling author of Train Your Mind, Change Your Brain
Emotional Styles and Anxiety

**Emotional Styles**
- Resilience
- Outlook
- Social Intuition
- Self Awareness
- Sensitivity to Context
- Attention

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Positive Psychology/Psychiatry

Introducing a New Theory of Well-Being

PERMA

Positive Emotions
Engagement
Positive Relationships
Meaning
Accomplishment
PERMA: How it Works

• Daily 10-minute evening mental exercises

• Remember and write 3 things that you have experienced. Describe how you felt

P  Pleasure, fun, joy, amusement
E  Engagement, attention with particular focus and not aware of surroundings, “in the moment”
R  Relationships – positive experiences with people
M  Meaning. Personally significant and meaningful
A  Accomplishment. Experiences where you felt successful or did something really well
RESILIENCE
Perseverance, no matter what the odds
Connor-Davidson Resiliency Scale (CD-RISC)

Please rate the following statements as they pertain to you, using the rating scale defined below:

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Able to adapt to change</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Close and secure relationships</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sometimes fate or God can help</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Can deal with whatever comes</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Past success gives confidence for new challenge</td>
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<tr>
<td>See the humorous side of things</td>
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<tr>
<td>Coping with stress strengthens</td>
<td></td>
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<tr>
<td>Tend to bounce back after illness or hardship</td>
<td></td>
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<tr>
<td>Things happen for a reason</td>
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<tr>
<td>Best effort no matter what</td>
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<td></td>
<td></td>
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<tr>
<td>You can achieve your goals</td>
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<tr>
<td>When things look hopeless, I don’t give up</td>
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<tr>
<td>Know where to turn for help</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Under pressure, focus and think clearly</td>
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<tr>
<td>Prefer to take the lead in problem solving</td>
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<tr>
<td>Not easily discouraged by failure</td>
<td></td>
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<tr>
<td>Think of self as strong person</td>
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<td></td>
<td></td>
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<tr>
<td>Make unpopular or difficult decisions</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Can handle unpleasant feelings</td>
<td></td>
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<tr>
<td>Have to act on a hunch</td>
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<tr>
<td>Strong sense of purpose</td>
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<tr>
<td>In control of your life</td>
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<td></td>
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<tr>
<td>I like challenges</td>
<td></td>
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<tr>
<td>You work to attain your goals</td>
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<td></td>
<td></td>
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<tr>
<td>Pride in your achievements</td>
<td></td>
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</tbody>
</table>

Adulthood Factors Promoting Resilience

- Optimism
- Cognitive reappraisal
- Active coping
- Social support
- Humor
- Physical exercise
- Prosocial behavior
- Mindfulness
- Moral compass

Clinical Perspective: 
Addressing Unmet Needs and Challenges in GAD

• Improvements in efficacy and tolerability of existing pharmacologic treatments
  – No clear guidelines in which agent to use for specific patient
  – Controversies and stigma in using BZD
• Need for naturalistic trials with “real world” patients with GAD and comorbid disorders (role of prevention)
• Embrace and advocate for a coordinated and integrative approach for treating GAD
• Screen and evaluate outcomes by using subjective and objective measurements
• **Aim High → Functional Recovery**
The Harvard Study of Adult Development: 
*Insights to Functionality and a Good Life*
The Harvard Study: *Conclusions on the Good Life*

1. Social Connections are Good for Us
2. Quality (not quantity) of Relationships
3. Good Relationships Protect Our Brain

*Relationships are the key to keep us Happy and Healthier*
There isn’t time, so brief is life for bickerings, apologies, heartburning, callings to accord, there is only time for loving and but an instant so to speak for that

Mark Twain