UNIVERSITY OF ALBERTA

Generalized Anxiety Disorder

Mental Health Assessment and Prescribing by Alberta Pharmacists (MAP-AP) Study Group

REB ID Pro00093776

Learning Objectives

1. Describe the epidemiology and the impacts of Generalized Anxiety Disorder (GAD)
2. Describe the diagnosis and clinical assessment for a patient with GAD
3. Describe patient administered monitoring tool (e.g., GAD-7) to manage GAD
4. Compare and contrast different pharmacotherapy options
5. Summarize the step-wise approach to managing GAD

Epidemiology

- GAD affects 1-4% of population worldwide

- In Canada:
  - Lifetime prevalence of GAD is 8.7%
  - In 2012, more than 700,000 (2.5%) Canadians aged 15+ experienced symptoms compatible with GAD in previous 12 months
  - 50% of GAD patients reported experiencing comorbid Major Depressive Episode (MDE)

Health Promotion and Chronic Disease Prevention in Canada, *37*(2), 54–62.

BMC Psychiatry, Vol. 14, p. S1.

Epidemiology

- Up to 40% of anxiety and related disorders are untreated
- Generally affects middle aged population: 35-54 years old
- Prevalence in females 3.2% vs. 2.0% in males
- Canadian born 2x more likely to experience GAD compared to immigrants

Health Promotion and Chronic Disease Prevention in Canada, *37*(2), 54–62.

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Impacts of GAD

- Quality of Life:
  - Significantly reduced global life satisfaction
  - More occupational impairment

- Occupational Costs:
  - GAD contributes to an average of 18.1 disability days in the previous 3 months

Journal of Affective Disorders, Vol. 140, pp. 103–112.

Impacts of GAD

- Economic burden:
  - Anxiety disorders (not GAD specific) mean total medical cost ~$6475/person USD

- Social impairment
  - Strain on personal and interpersonal relationships

Journal of Affective Disorders, Vol. 140, pp. 103–112.

When does anxiety become a disorder?

- Increase in intensity/duration that is more than usual based on circumstance
- **Leads to impairment and decrease in QOL**
- Disrupts social and interpersonal functioning in an attempt to decrease anxiety
- Clinically significant and unexplained physical symptoms

How is GAD diagnosed?

A. Excessive anxiety and worry (occurring more days than not for at least for 6 months) about a number of events or activities
B. Difficulty controlling worry
C. Disturbance causes clinically significant distress or functional impairment
D. Associated with 3 or more of the following:
    a. Restlessness or feeling keyed up or on edge
    b. Being easily fatigued
    c. Difficulty concentrating or mind going blank
    d. Irritability
    e. Muscle tension
    f. Sleep disturbance
E. Disturbance not due to physiological effects of a substance or another medical condition
F. Disturbance is not better explained by another mental disorder (DSM-5)

Anxiety and related disorders

Table 8 Key features of specific anxiety and related disorders

Disorder	Key features
Panic disorder	• Recurrent unexpected panic attacks, in the absence of triggers • Persistent concern about additional panic attacks and/or maladaptive change in behavior related to the attacks
Agoraphobia	• Marked, unreasonable fear or anxiety about a situation • Active avoidance of feared situation due to thoughts that escape might be difficult or help unavailable if panic-like symptoms occur
Specific phobia	• Marked, unreasonable fear or anxiety about a specific object or situation, which is actively avoided (e.g., flying, heights, animals, receiving an injection, seeing blood)
Social anxiety disorder (SAD)	• Marked, excessive or unrealistic fear or anxiety about social situations in which there is possible exposure to scrutiny by others • Active avoidance of feared situation
Generalized anxiety disorder (GAD)	• Excessive, difficult to control anxiety and worry (apprehensive expectation) about multiple events or activities (e.g., school/work difficulties) • Accompanied by symptoms such as restlessness/feeling on edge or muscle tension
Obsessive–compulsive disorder (OCD)	• Obsessions: recurrent and persistent thoughts, urges, or images that are experienced as intrusive and unwanted and that cause marked anxiety or distress • Compulsions: repetitive behaviors (e.g., hand washing) or mental acts (e.g., counting) that the individual feels driven to perform to reduce the anxiety generated by the obsessions
Posttraumatic stress disorder (PTSD)	• Exposure to actual or threatened death, serious injury, or sexual violation • Intrusion symptoms (e.g., distressing memories or dreams, flashbacks, intense distress) and avoidance of stimuli associated with the event • Negative alterations in cognitions and mood (e.g., negative beliefs and emotions, detachment), as well as marked alterations in arousal and reactivity (e.g., irritable behavior, hypervigilance)

Adapted from reference [26].

GAD: Risk Factors

- Family Hx of GAD
- Personal Hx of anxiety or mood disorder
- Childhood stressful life events or trauma
- Being female
- Chronic medical illness
- Behavioural inhibition
- Comorbid psychiatric disorders: Substance Use Disorder, Bipolar Disorder, Major Depressive Disorder, ADHD

GAD: Assessment

- Obtain the following information at baseline:
  1. Review of systems
  2. PMHx
  3. Medications: prescribed, OTC
  4. Family Hx: anxiety, mood disorder
  5. Social Hx: EtOH use, caffeine intake, illicit drug use
  6. Labs: CBC, Lipid profile, lytes, TSH, LFTs, FBG
  7. If warranted, urine toxicology screen for substance use

GAD: Screening Questions

- As screening questions to patients at risk of GAD

- During the past 2 weeks how much have you been bothered by the following problems?
  1) Feeling nervous, anxious, frightened, worried, or on edge?
  2) Feeling panic or being frightened?
  3) Avoiding situations that make you anxious?

Assessment: Medication Hx

- Several medications are associated anxiety symptoms

Anticonvulsants	Carbamazepine, phenytoin
Antidepressants	SSRI, TCAs
Antihypertensives	Felodipine, clonidine
Antibiotics	Quinolones, isoniazid
Bronchodilators	Salbutamol, theophylline
Corticosteroids	Prednisone
Dopamine agonists	Levodopa
Herbals	Ma Huang, ginseng, ephedra

Assessment: Medication Hx

- Several medications are associated anxiety symptoms

Illicit substances	Marijuana, ecstasy
NSAIDs	Ibuprofen
Sympathomimetics	Pseudoephedrine, phenylephrine
Thyroid hormones	Levothyroxine
Toxicity	Anticholinergics, antihistamines, digoxin
Withdrawal	Alcohol, sedatives

Patient Monitoring Tool for GAD: GAD-7

- Generalized Anxiety Disorder-7
- GAD-7 screener objectively determines initial symptom severity and monitor changes/effect of treatment over time
- 7 Items/Questions
  - Patient Self Administered
  - Each item scored out of 3
  - Reviews criteria that has bothered the patient in the past 2 weeks
  - Expected completion ≤ 3 minutes
- Validated for GAD
  - 89% sensitivity
  - 82% specificity
  - Retest reliability with ICC=0.83

- Useful in primary care and mental health settings to allow rapid screening for presence of clinically significant anxiety disorder

Archives of Internal Medicine, *166*(10), 1092–1097.

GAD-7: Items

Over the last two weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid, as if something awful might happen	0	1	2	3

Column totals _____ + _____ + _____ + _____ =

Total score _____

If you checked any problems, how difficult have they made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

The last question of the GAD-7 is an indicator of global impairment

GAD-7: Scoring

Score	Interpretation of GAD-7
0-4	None
5-9	Mild anxiety
10-14	Moderate anxiety ≥10 possible diagnosis of GAD; confirm by further evaluation
15-21	Severe anxiety

GAD: Goals of Therapy

Short-Term (8-12 weeks since the initial diagnosis)	Maintenance Phase (>3 months, once patient reached remission)
Minimize severity, duration, and frequency of Sx Minimize disruption to function Full remission (12+ weeks)	Restoration to full function Prevent relapse Maintain stable mood/ coping abilities
At all phases...	
Prevent consequence(s) of illness Prevent/ minimizes adverse effects of medications	

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GAD: General Approach to Treatment

- Identify GAD: impairing function +/- quality of life
- Consider comorbid medical conditions or mood disorders
- Consider pharmacological or psychological therapy
  - Psychotherapy: Cognitive Behavioural Therapy (CBT)
  - Drug therapy
- Choice of treatment
  - Patient preference
  - Available resources
  - Patient prior to treatment

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GAD: Non-pharmacological Treatments

- CBT markedly effective
  - Comparable to pharmacotherapy
  - Group and individual therapy both effective - individual therapy may show quicker response

- Psychological and pharmacological treatment
  - Combination may be beneficial

- Weight-lifting or aerobic exercise showed significant symptomatic improvements

- Bright light therapy is not recommended

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GAD: Pharmacological options

- First line: SSRIs & SNRIs and Pregabalin
  - Head to head trials seem to have similar effectiveness

Table 24 Recommendations for pharmacotherapy for GAD

First-line	Agomelatine, duloxetine, escitalopram, paroxetine, paroxetine CR, pregabalin, sertraline, venlafaxine XR
Second-line	Alprazolam*, bromazepam*, bupropion XL*, buspirone, diazepam*, hydroxyzine, imipramine, lorazepam*, quetiapine XR*, vortioxetine
Third-line	Citalopram, divalproex chrono, fluoxetine, mirtazapine, trazodone
Adjunctive therapy	**Second-line:** pregabalin **Third-line:** aripiprazole, olanzapine, quetiapine, quetiapine XR, risperidone **Not recommended:** ziprasidone
Not recommended	Beta blockers (propranolol), pexacerfont, tiagabine

CR = controlled release; XL = extended release; XR=extended release.

*Note: These have distinct mechanisms, efficacy and safety profiles. Within these second-line agents, benzodiazepines would be considered first in most cases, except where there is a risk of substance abuse, while bupropion XL would likely be reserved for later. Quetiapine XR remains a good choice in terms of efficacy, but given the metabolic concerns associated with atypical antipsychotic, it should be reserved for patients who cannot be provided antidepressants or benzodiazepines. Please refer to text for further rationale for the recommendations.

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GAD: Pharmacological options

- Second line: Benzodiazepines, TCAs and Others
    - Benzodiazepines: demonstrated efficacy; however, only recommended for short-term use due to side effects, dependence, and withdrawal issues
    - TCAs: demonstrated efficacy; however, increased risk of toxicity and side effects
    - Bupropion XL: similar efficacy as escitalopram but limited data
    - Vortioxetine: may be useful
    - Quetiapine: demonstrated efficacy; however, more sedation, weight gain, and high dropout rates due to adverse events
    - Buspirone: similar efficacy as benzodiazepines and possibly SSRIs but limited data
    - Hydroxyzine: similar efficacy to benzodiazepines but limited clinical experience

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GAD: Pharmacological options

- Third line: Citalopram, fluoxetine, paroxetine CR, mirtazapine, trazodone
  - Demonstrated benefit, although lower quality trials

- Adjunctive Therapies:
  - Considered in treatment resistant GAD, to be added to current therapy
  - Second line: Pregabalin
  - Third line: Atypical antipsychotics

- Long-term therapy is recommended to prevent relapse

GAD: Pharmacological options

Table 23 Strength of evidence for pharmacotherapy for GAD

Agent	Level of evidence	Agent	Level of evidence
Antidepressants			
SSRIs		**TCAs**	
Escitalopram [544-552]	1	Imipramine [553,581-583]	1
Paroxetine [546,547,553-558]	1	**Other antidepressants**	
Sertraline [556,559-561]	1	Agomelatine [584,585]	1
Citalopram [562]	3	Vortioxetine [586,587]	1*
Fluoxetine [563]	3	Bupropion XL [549]	2
Paroxetine CR [564,565]	3	Trazodone [583]	2
SNRIs		Mirtazapine [588]	3
Duloxetine [566-571]	1		
Venlafaxine XR [548,553,570-580]	1		

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GAD: Pharmacological options

Other therapies

Anxiolytics		**Atypical antipsychotics**	
Benzodiazepines		Quetiapine XR [551,557,602,603]	1
Alprazolam [589-593]	1	Adjunctive quetiapine [565,604,605]	1*
Bromazepam [589,594]	1	Adjunctive risperidone [606,607]	1*
Diazepam [583,589,595,596]	1	Adjunctive olanzapine [608]	2
Lorazepam [589,593,597-601]	1	Adjunctive aripiprazole [269,609]	3
		Adjunctive quetiapine XR [610]	3
		Adjunctive or monotx ziprasidone [611,612]	2 (-ve)
Anticonvulsants		**Other treatments**	
Pregabalin [576,577,592,593,597,613]	1	Buspirone [108,561,572,589,598,618,619]	1
Divalproex chrono [614]	2	Hydroxyzine [594,619,620]	1
Tiagabine [615,616]	1 (-ve)	Pexacerfont [552]	2 (-ve)
Adjunctive pregabalin [617]	2	Propranolol [621]	2 (-ve)
		Memantine [622]	4 (-ve)

*Conflicting data. SNRI = serotonin–norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; XL = extended release; XR=extended release; (-ve) = negative.

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New Agents for GAD?

- CANMAT Guidelines (2014) did not include newer agents
- Limited evidence for use of vortioxetine, vilazodone, and levomilnacipran in GAD
- Vortioxetine has the best evidence; however, none of the above have the indication for GAD (MDD only)

GAD: Monitoring response

- Start with a low dose and titrate to effect (doses may be higher than that used in MDD) (CANMAT)
- Utilize GAD-7 and Global Impression Scale to monitor response and effectiveness
- Increase dose every 1-2 weeks depending on tolerability
- Delayed onset of 2-8 weeks for symptom relief/onset

GAD: Monitoring response

Level of Response	% Reduction from Baseline Rating Scale Score
Response	≥ 50%
Partial Response	25-49%
Remission	Loss of diagnostic status (e.g., GAD-7 <5) No functional impairment

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Monitoring: Common adverse effects

CNS	Headache, dizziness somnolence, insomnia
PSYCH	Nervousness, anxiety, agitation
HEENT	Dry mouth
GI/GU	Nausea, constipation, anorexia
MSK	Tremor

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Monitoring: Medication-Specific Adverse Effects

Table 7. Prevalence of Adverse Events among Newer Antidepressants: Unadjusted Frequency (%) of Common Adverse Events as Reported in Product Monographs.

	Nausea	Constipation	Diarrhea	Dry Mouth	Headaches	Dizziness	Somnolence	Nervousness	Anxiety	Agitation	Insomnia	Fatigue	Sweating	Asthenia	Tremor	Anorexia	Increased Appetite	Weight Gain	Male Sexual Dysfunction
Citalopram	21		8	19				3	3	2		5	11		8	4			9
Escitalopram	15	4	8	7	3	6	4	2	2		8	5	3		2		2	2	10
Fluoxetine	21			10			13	14	12		16		8	9	10	11			2
Fluvoxamine	37	18	6	26	22	15	26	2	2	16	14		11	5	11	15			1
Paroxetine	26	14	11	18	18	13	23	5	5	2	13		11	15	8		1		16
Sertraline[a]	26	8	18	16	20	12	13	3	3	6	16	11	8		11	3	1		16
Desvenlafaxine[b]	22	9		11		13	4	<1	3		9	7	10		2				6
Duloxetine	20	11	8	15		8	7		3		11	8	6		3				10
Levomilnacipran	17	9		10	17	8			2		6		9						11
Milnacipran	12	7		9	10				4		7	3	4		3				
Venlafaxine IR	37	15	8	22	25	19	23	13	6	2	18		12	12	5	11			18
Venlafaxine XR	31	8	8	12	26	20	17	10	2	3	17		14	8	5	8			16
Agomelatine[c]	C	C	C		C	C	C		C		C	C	C						
Bupropion SR[d]	11	7	4	13	28	7	3	5	5	2	8		2	2	3				
Bupropion XL	13	9		26	34	6			5	2	16				3				
Mirtazapine		13		25		7	54							8	7		17	12	
Moclobemide	5	4	2	9	8	5	4	4	3	5	7	3	2	1	5				
Vilazodone[e]	24		29	7	14	8	5				6	3					3	2	5
Vortioxetine[f]	23	4	5	6		5	3				3	3	2						<1

When data from multiple doses were reported separately, the data from the minimum therapeutic dose were used (indicated by footnotes). Data sources and references are available in Supplemental Table S3. Clear cells represent 0% to 9%; shaded cells, 10% to 29%; and black cells, 30% and higher.

[a]Data from all indications.
[b]Data from 50-mg dose.
[c]C, common effects, ≥1% and <10%.
[d]Data from 100- to 150-mg dose.
[e]Data from 40-mg dose.
[f]Data from 10-mg dose.

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