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Medical Marijuana for the Treatment of Generalized Anxiety Disorder: An Evidence Review

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Introduction

Purpose of evidence review

This review evaluates evidence on cannabis use in adults for the treatment of generalized anxiety disorders. The Arizona Department of Health Services (ADHS), funded this report, to assist in assessing anxiety disorders as a condition to add to those that qualify for the use of medical marijuana in Arizona.

Background

Pursuant to A.R.S. § 36-2801.01, the public may petition the Arizona Department of Health Services (ADHS) to add debilitating medical conditions to those listed in A.R.S. 36-2801(3). The ADHS established the manner in which it shall consider petitions to add debilitating medical conditions in A.A.C. R9-17-106. A.A.C. R9-17-106(C) states, ADHS “shall accept requests for the addition of a medical condition to the list of debilitating medical conditions in R9-17-201 in January and July of each calendar year starting in January 2012”. After receiving requests for adding conditions the ADHS requests a report on the scientific evidence on the use of cannabis for this condition from the University of Arizona College of Public Health. In addition the Department holds a public hearing to hear public testimony on the condition and its treatment with cannabis. The Department Medical Advisory Committee then considers the totality of the evidence in deciding to add a condition to the list, or not.

Scope of evidence review

List of Key Questions

Benefits and harms of cannabis therapy for generalized anxiety disorders

1. What are the benefits (short and long-term benefits) of cannabis use for those with anxiety disorders?
2. What are the harms (short and long-term harms) of cannabis use for anxiety disorder patients?
3. What are the benefits and harms of cannabis for treating anxiety disorder in patients with a history of substance abuse or addiction that are undergoing treatment for addiction?

Conflict of Interest

None of the reviewers conducting this review have any conflicts of interest to disclose.

Methods

Dates of Search

May 2012 - June 2012

Population

Adults (≥ 18 years old)

Literature search and strategy

The topics of cannabis use and anxiety disorder were searched in the following databases: The Cochrane Library, Ovid MEDLINE® and PsycINFO. Bibliographies of articles identified through databases were hand searched for pertinent articles. In addition, there was a gray literature search using Google Scholar to identify electronically published articles and current unpublished studies. A detailed description of each search can be found in Appendix 1.

Inclusion and exclusion criteria

All identified studies were imported into an electronic database (RefWorks) and considered for inclusion. We included studies that met all of the following criteria:

1. Evaluated adults (≥ 18 years old) with anxiety disorder
2. English language
3. Human study
4. Were relevant to one of the Key Questions

Excluded articles included those that were:

1. Animal studies
2. Experiments on biochemical or pathophysiological pathways
3. Case reports or case series
4. Editorials or opinions
5. Not addressing a key question.

Data synthesis

Observational studies were assessed using the main domains described in tools commonly used (Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovich C, Song F, et al. Evaluating non-randomized intervention studies. *Health Technology Assessment* 2003;7(27)). The overall quality of the evidence is ranked using GRADE methodology demonstrated in Appendix 2. (Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions. In: Agency for Healthcare Research and Quality. *Methods Guide for Comparative Effectiveness Reviews*. Rockville, MD. Available at: <http://effectivehealthcare.ahrq.gov/healthInfo.cfm?infotype=rr&ProcessID=60>.)

Results

Findings

A total of 261 articles were identified. The table #1 below lists 26 articles, which came the closest to addressing any of the key questions. The excluded articles are listed in Appendix 3.

Article , Citation and Database	Description and Design of Study	Findings	Quality
1. Agosti V, Nunes E, Levin F. Rates of psychiatric	Cross sectional study using	Those with cannabis	Very low quality

<p>co morbidity among U.S. residents with lifetime cannabis dependence. Am J Drug Alcohol Abuse. 2002 Nov;28(4):643-52.</p>	<p>a large national data set and representative sample, the national co morbidity survey. N=5877</p>	<p>dependence had a 12% lifetime prevalence of anxiety with an odds ratio of 2.7. Much higher prevalence of other mental disorders.</p>	<p>Recall bias, series of single variable analyses not controlling for other potential confounders.</p>
<p>2. Crippa JA, Zuardi AW, Martin-Santos R, Bhattacharyya S, Atakan Z, McGuire P, et al. Cannabis and anxiety: A critical review of the evidence. Hum Psychopharmacol. 2009 Oct;24(7):515-23.</p>	<p>Systematic review</p>	<p>Anxiety can occur as a result of cannabis use. The prevalence of anxiety is higher in cannabis users and vice versa. No cause and effect can be attributed.</p>	<p>Low quality review. No system for assessing the quality of studies or ranking of overall evidence. No combination of study results in forest plot.</p>
<p>3. Degenhardt L, Hall W, Lynskey M. Alcohol, cannabis and tobacco use among australians: A comparison of their associations with other drug use and use disorders, affective and anxiety disorders, and psychosis. Addiction. 2001 Nov;96(11):1603-14.</p> <p>Note: this and the next study appear to be the same, with a slightly different analysis.</p>	<p>Cross-Sectional Study. Data from the Australian National Survey of Mental Health and Well-Being was analyzed (N=10,641).</p>	<p>After controlling for demographics, neuroticism and other drug use, cannabis was not associated with anxiety or affective disorders.</p>	<p>Low-to-moderate quality A large representative sample from Australia. Major potential confounders were controlled for. Large potential for recall bias from survey participants. Self-reported behaviors.</p>
<p>4. Degenhardt L, Hall W, Lynskey M. The relationship between cannabis use, depression and anxiety among australian adults: Findings from the national survey of mental health and well-being. Soc Psychiatry Psychiatr Epidemiol. 2001 May;36(5):219-27.</p>	<p>Cross-Sectional Study. Data from the Australian National Survey of Mental Health and Well-Being was analyzed (N=10,641).</p>	<p>There was a moderate association between cannabis use in the past 12 months and the prevalence of affective and anxiety disorders. Cannabis use did not appear to be directly related to depression or anxiety when other drug use was considered as contributing factors.</p>	<p>Low-to-moderate quality A large representative sample from Australia. Major potential confounders were controlled for. Large potential for recall bias from survey participants. Self-reported behaviors.</p>
<p>5. Fabre LF, McLendon D. The efficacy and safety of nabilone (a synthetic cannabinoid) in the treatment of anxiety. J Clin Pharmacol. 1981 Aug-Sep;21(8-9 Suppl):377S-82S.</p>	<p>Two clinical trials. 5 patients in an open label trial of nabilone, a synthetic cannabinoid, but not a THC. 20 patients in double blind trial;10 on nabilone 10 on placebo. Method of allocation not mentioned. All patients had psychoneurotic anxiety and were at one clinic in Texas.</p>	<p>Patients on nabilone showed significant improvement in several measures of anxiety.</p>	<p>Low-to moderate quality Small study, allocation method not clear. Dosage information very unclear</p>
<p>6. Szuster RR, Pontius EB, Campos PE. Marijuana sensitivity and panic anxiety. J Clin Psychiatry. 1988 Nov;49(11):427-9.</p>	<p>Cross sectional study of a group of 25 attending outpt clinic in Hawaii with dx of panic disorder or agoraphobia with panic attacks. Control group A were 22 with dx of depression. Control group B were 25 staff at the hospital.</p>	<p>Those with panic attacks reported being anxious with marijuana use (14/22 than others 2/38).</p>	<p>Very low quality Biased sample. Subject to recall bias. "controls" not selected randomly.</p>
<p>7. Tepe E, Dalrymple K, Zimmerman M. The impact of comorbid cannabis use disorders on the clinical presentation of social anxiety disorder. J Psychiatr Res. 2012 Jan;46(1):50-6.</p>	<p>Cross sectional study in Rhode Island of 873 patients of an outpatient psychiatry clinic with a social anxiety disorder. 173 also had a cannabis use disorder.</p>	<p>Those with cannabis use disorder were more likely to have a lifetime diagnosis of PTSD and specific phobia and lifetime substance use disorders (including alcohol) and were also more likely to report better physical health, and fewer limitations</p>	<p>Low quality Biased sample, psychiatry clinic patients. Potential confounders were controlled for. Interviews conducted by students.</p>

		related to their physical health. The odds ratios were very low with lower confidence intervals close to 1.0.	
8. Tournier M, Sorbara F, Gindre C, Swendsen JD, Verdoux H. Cannabis use and anxiety in daily life: A naturalistic investigation in a non-clinical population. <i>Psychiatry Res.</i> 2003 May 1;118(1):1-8.	Cross sectional 689 college students who attended a psychology class were interviewed and of these 79 selected to participate in survey based on level of marijuana use.	There was no association between marijuana use and anxiety.	Low quality. Non random sample, university students only, self reported behavior and symptoms. There was use of statistical methods to control for potential confounders.
9. Arendt M, Rosenberg R, Foldager L, Perto G, Munk-Jorgensen P. Psychopathology among cannabis-dependent treatment seekers and association with later substance abuse treatment. <i>J Subst Abuse Treat.</i> 2007 Mar;32(2):113-9.	Retrospective cohort in Denmark of 3114 seeking treatment for cannabis dependence between 1996 and 2002 and 15,570 controls.	Those seeking treatment for cannabis dependence had higher rates of many mental disorders including schizophrenia, bipolar and affective disorders.	Low to moderate quality Biased sample. Only those seeking treatment for dependence were included in the cohort and findings do not apply to those who use recreationally. It is likely that subjects with other severe disorders would be more likely to seek treatment.
10. Bonn-Miller MO, Zvolensky MJ, Johnson KA. Uni-morbid and co-occurring marijuana and tobacco use: examination of concurrent associations with negative mood states. <i>J Addict Dis</i> 2010;29:68-77.	Cross sectional study of 250 adult volunteers in Vermont. 4 groups studied, tobacco users, marijuana users, users of both and users of neither.	Tobacco use resulted in greater negative affect and more anxiety than marijuana use and non use of either. It is not clear how clinically significant the findings on these scales are.	Low quality Very biased sample. Interviewed on person. Scales with validity used. Some confounders controlled for.
11. Buckner JD, Bonn-Miller MO, Zvolensky MJ, Schmidt NB. Marijuana use motives and social anxiety among marijuana-using young adults. <i>Addict Behav.</i> 2007 Oct;32(10):2238-52.	Cross sectional study of 159 female college students.	Social anxiety was associated with marijuana use problems but not frequency of use.	Low quality Biased sample. Recall bias likely. Standardized tools were used for data collection and classifications and some confounding variables were controlled for.
12. Buckner JD, Crosby RD, Wonderlich SA, Schmidt NB. Social anxiety and cannabis use: An analysis from ecological momentary assessment. <i>J Anxiety Disord.</i> 2012 Mar;26(2):297-304.	Cohort study of 49 college students who were recruited on campus. They were contacted by PDA 6 times a day, randomly for 2 weeks and asked about anxiety and cannabis craving.	Individuals with higher social anxiety and craving were most likely to use cannabis, especially if others were using.	Moderate quality Biased sample of heavy users. Innovative study design that tested participants in real life setting. Small sample
13. Buckner JD, Zvolensky MJ, Smits JA, Norton PJ, Crosby RD, Wonderlich SA, et al. Anxiety sensitivity and marijuana use: An analysis from ecological momentary assessment. <i>Depress Anxiety.</i> 2011 May;28(5):420-6.	Cohort study of 49 college students who were recruited on campus. They were contacted by PDA 6 times a day, randomly for 2 weeks and asked about anxiety and cannabis craving.	Greater fear of anxiety was associated with greater severity of cannabis related problems.	Moderate quality Biased sample of heavy users. Innovative study design that tested participants in real life setting. Small sample.
14. Cheung JT, Mann RE, Ialomiteanu A, Stoduto G, Chan V, Ala-Leppilampi K, et al. Anxiety and mood disorders and cannabis use. <i>Am J Drug Alcohol Abuse.</i> 2010 Mar;36(2):118-22.	Cross sectional study. Data from the Centre for Addiction and Mental Health (CAMH) Monitor survey was analyzed (N=14,531).	Anxiety and mood disorders were most common among heavy cannabis users (used almost every day or more) (18.1%) and lowest for abstainers (8.7%).	Low quality A large representative sample from Ontario. Subject to recall bias. The major problem is that anxiety and mood disorders are combined as a singlediagnosis.
15. de Dios MA, Hagerty CE, Herman DS, Hayaki J, Anderson BJ, Budney AJ, et al. General anxiety disorder symptoms, tension reduction, and marijuana use among young adult females. <i>Journal of Women's Health.</i> 2010 09;19(9):1635-42.	Data used from a randomized clinical trial in Rhode Island (N=332). However, the data for this study was collected at one sitting and is really a cross sectional study.	Anxiety symptoms had a direct effect on tension reduction expectancies and an indirect effect on marijuana use. Relationship were relatively weak.	Low-to-moderate quality All female sample compromises generalizability. Recall bias possible. Some confounders controlled for through a modeling method.

16. Gilder DA, Lau P, Dixon M, Corey L, Phillips E, Ehlers CL. Co-morbidity of select anxiety, affective, and psychotic disorders with cannabis dependence in southwest california indians. J Addict Dis. 2006;25(4):67-79.	Cross sectional study American Indian sample from California was (N=513).	SWC Indians in this sample had high rates of cannabis dependence (43% in men and 24% in women), cannabis-induced psychiatric disorders each occurred in 1% or less of the sample. No significant co-morbidity with independent psychiatric disorders was found.	Very low quality. Recruited sample was very selective. 15% of sample had anxiety (in this study anxiety was grouped as being panic disorder with or without agoraphobia, agoraphobia without panic, social phobia, and obsessive-compulsive disorder), A series of single variable analyses.
17. van Laar M, van Dorsselaer S, Monshouwer K, de Graaf R. Does cannabis use predict the first incidence of mood and anxiety disorders in the adult population? Addiction. 2007 Aug;102(8):1251-60.	Cohort study Data from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). The analysis was carried out on 3881 people who had no life-time mood disorders and on 3854 people who had no life-time anxiety disorders at baseline.	None of the associations between cannabis use and anxiety disorders remained significant after adjustment for confounders.	Low-to-moderate quality Confounding variables were controlled for. Self-reported use of cannabis.
18. Wittchen HU, Frohlich C, Behrendt S, Gunther A, Rehm J, Zimmermann P, et al. Cannabis use and cannabis use disorders and their relationship to mental disorders: A 10-year prospective-longitudinal community study in adolescents. Drug Alcohol Depend. 2007 Apr;88 Suppl 1:S60-70.	Longitudinal cohort design. Data was collected as part of the Early Developmental Stages of Psychopathology (EDSP) study. Baseline survey in 1995 had N=1395, response rate 74.6%. With three follow-up examinations taking place 1.5, 4 and 10 years later.	CUD significant associations were found for GAD (OR: 3.9; CI: 1.1-13.7)	Low-to-moderate quality The representation of participants with GAD was small (at baseline <1%).
19. Buckner JD, Heimberg RG, Schmidt NB. Social anxiety and marijuana-related problems: The role of social avoidance. Addict Behav. 2011 Jan-Feb;36(1-2):129-32.	Cross sectional study of 102 college students who were marijuana users and received college credit for participating.	Social avoidance was associated with marijuana related problems.	Low quality Biased sample, small numbers. Some confounders were controlled for. Validated instruments used for data collection and classification
20. Buckner JD, Mallott MA, Schmidt NB, Taylor J. Peer influence and gender differences in problematic cannabis use among individuals with social anxiety. J Anxiety Disord. 2006;20(8):1087-102.	Cross sectional study of 123 college students paid for participation.	Social anxiety was associated with cannabis abuse with gender and peer substance abuse affecting the relationship.	Low quality Biased sample, small sample. Recall bias. Some confounders controlled for.
21. Buckner JD, Schmidt NB, Bobadilla L, Taylor J. Social anxiety and problematic cannabis use: Evaluating the moderating role of stress reactivity and perceived coping. Behav Res Ther. 2006 Jul;44(7):1007-15.	Cross sectional study of 123 college students paid for participation.	Social anxiety was associated with cannabis abuse.	Low quality Biased sample, small sample. Recall bias. Some confounders controlled for.
22. Buckner JD, Silgado J, Schmidt NB. Marijuana craving during a public speaking challenge: Understanding marijuana use vulnerability among women and those with social anxiety disorder. J Behav Ther Exp Psychiatry. 2011 Mar;42(1):104-10.	Controlled experiment. 60 college students who used marijuana regularly recruited. Half were assigned to a non anxiety provoking activity and the other half to an anxiety provoking activity. Marijuana craving was measured.	The anxiety provoking activity produced more marijuana craving among women and those with social anxiety disorder.	Moderate to Low quality Small biased sample. Marijuana craving not marijuana use measured.
23. Buckner JD, Schmidt NB, Lang AR, Small JW, Schlauch RC, Lewinsohn PM. Specificity of social	Longitudinal cohort of adults in Oregon. Followed	Those without cannabis use at first interview ,	Moderate quality

anxiety disorder as a risk factor for alcohol and cannabis dependence. J Psychiatr Res. 2008 Feb;42(3):230-9.	from end of high school through age 30. Assessed 4 times over the years. Those without cannabis use at first interview , with social anxiety disorder were 6 times as likely to develop cannabis dependence (but not abuse) as those without social anxiety.	with social anxiety disorder were 6 times as likely to develop cannabis dependence (but not abuse) as those without social anxiety. Same association with alcohol dependence.	Hard to tell what the loss to follow up was. Good use of standardized tools . Analyses were all single variable, not controlling for confounders.
24. Buckner JD, Schmidt NB. Marijuana effect expectancies: Relations to social anxiety and marijuana use problems. Addict Behav. 2008 Nov;33(11):1477-83.	Cross sectional study of 337 college students who received course credit for participating.	A somewhat complex analysis of different expectancies and relationship to social anxiety and marijuana use. Some statistically significant relationships were found but the odds ratios were extremely low.	Low quality Biased sample, recall bias possible. Confounders were controlled for. Standard tools for data collection and classification.
25. Bergamaschi MM, Queiroz RH, Chagas MH, de Oliveira DC, De Martinis BS, Kapczinski F, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients. Neuropsychopharmacology. 2011 May;36(6):1219-26.	Controlled clinical trial, Double blind. 24 subjects with generalized social anxiety disorder randomized to receive cannabidiol or placebo, and 12 healthy controls. Intervention was given prior to having to make a speech. Anxiety measured by self reported symptoms and by physiological measurements.	Cannabidiol reduced anxiety, cognitive impairment and discomfort.	High quality Very nice little study. The subjects were Brazilian college students. The results should be considered preliminary and in need of confirmation. The intervention was not marijuana but a non psychomimetic compound, which allowed for the double blind design.
26. Buckner JD, Schmidt NB. Social anxiety disorder and marijuana use problems: The mediating role of marijuana effect expectancies. Depress Anxiety. 2009;26(9):864-70.	Cross sectional study of 107 college students. 26% has social anxiety disorder.	Social anxiety associated with marijuana use problems after controlling for confounders.	Low quality Biased small sample. Recall bias of self reported marijuana use. Confounders controlled for.

Summaries

Summary of gray literature

The gray literature search was unproductive beyond the databases already searched. . Many articles recommend further research and evaluation of the co-occurrence of anxiety disorders and cannabis use.

Summary of articles provided with public petition to ADHS

The nine articles were provided by the public are summarized in the table below.

Article	Description	Limitations
1. Braidă, D.; Limonta, V.; Malabarba, L.; Zani, A.; Sala, M. 5-HT _{1A} receptors are involved in the anxiolytic effect of Delta ⁹ -tetrahydrocannabinol and AM 404, the anandamide transport inhibitor, in Sprague-Dawley rats. Eur. J. Pharmacol., 2007, 555, 156-163.	Animal Study	Not assessed.
2. Berrendero, F.; Maldonado, R. Involvement of the opioid system in the anxiolytic-like effects induced by Delta ⁹ -tetrahydrocannabinol. Psychopharmacology (Berl.), 2002, 163, 111-117.	Animal Study	Not assessed.

3. Crean RD, Crane NA, Mason BJ. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. <i>J Addict Med.</i> 2011 Mar;5(1):1-8.	This article is a review of the research on the acute, residual, and long-term effects of cannabis use on executive functions and discusses the implications for treatment.	Anxiety disorders were not discussed in this article.
4. Jiang, W.; Zhang, Y.; Xiao, L.; Van Cleemput, J.; Ji, S.P.; Bai, G.; Zhang, X. Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects. <i>J. Clin. Invest.</i> , 2005, 115, 3104-3116.	Animal Study	Not assessed.
5. Moreira, F.A.; Aguiar, D.C.; Guimaraes, F.S. Anxiolytic-like effect of cannabinoids injected into the rat dorsolateral periaqueductal gray. <i>Neuropharmacology</i> , 2007, 52, 958-965.	Animal Study	Not assessed.
6. Phan, K.L.; Angstadt, M.; Golden, J.; Onyewuenyi, I.; Popovska, A.; de Wit, H. Cannabinoid modulation of amygdala reactivity to social signals of threat in humans. <i>J. Neurosci.</i> , 2008, 28, 2313-2319.;	Experiment on biochemical pathways	Not assessed.
7. Rodriguez de Fonseca, F.; Rubio, P.; Menzaghi, F.; Merlo-Pich, E.; Rivier, J.; Koob, G.F.; Navarro, M. Corticotropin-releasing factor (CRF) antagonist [D-Phe12,Nle21,38,C alpha MeLeu37]CRF attenuates the acute actions of the highly potent cannabinoid receptor agonist HU-210 on defensive-withdrawal behavior in rats. <i>J. Pharmacol. Exp. Ther.</i> , 1996, 276, 56-64.;	Animal Study	Not assessed.
8. Sethi, B.B.; Trivedi, J.K.; Kumar, P.; Gulati, A.; Agarwal, A.K.; Sethi, N. Antianxiety effect of cannabis: involvement of central benzodiazepine receptors. <i>Biol. Psychiatry</i> , 1986, 21, 3-10.;	Animal Study	Not assessed.
9. Solowij N, Stephens RS, Roffman RA, Babor T, et al. Cognitive functioning of long-term heavy cannabis users seeking treatment. <i>JAMA.</i> 2002 Mar 6;287(9):1123-31.	Cross sectional study of 102 daily cannabis users in the U.S.	Addresses effects of daily use of recreational marijuana, not use for medical purposes. Small study, biased sample.

Conclusions

There were no studies that directly addressed the key questions. Two clinical trials of moderate to high quality found some benefit of non THC cannabinoids (nabilone and cannabidiol) among a small number of study participants. These are interesting studies with findings not entirely pertinent to the issue of using medical marijuana. There are a fair number of cross sectional and cohort studies that look at the co morbidity of marijuana dependence and abuse with anxiety of some form, either social anxiety disorder, situational anxiety or panic attacks. These studies have conflicting results; some finding an association, others not. These studies are of interest but do not directly address the key questions. The analysis of this body of literature is complex and complicated by differing definitions of anxiety, different methods of measuring cannabis use, concentrating on cannabis abuse and dependence, and using biased samples. This review should not be considered a complete systematic review of this topic. This initial review indicates that anxiety disorders and marijuana use may be related but does not answer the question of whether this is beneficial or harmful for those that self medicate. And, it is possible that anxiety disorders are also associated with other substance use, such as alcohol. This review did not address that question.

Current Recommended Treatments for Anxiety Disorders

A search was conducted of the Clinical Guideline Clearinghouse for treatment guidelines for anxiety disorders. Below is a list of the guidelines. See Appendix 4.

- National Collaborating Centre for Mental Health, National Collaborating Centre for Primary Care. Generalized anxiety disorder and panic disorder (with or without agoraphobia) in adults. Management in primary, secondary and community care. London (UK): National Institute for Health and Clinical Excellence (NICE); 2011 Jan. 56 p. (Clinical guideline; no. 113). Retrieved on June 21, 2012 from <http://guidelines.gov/content.aspx?id=34280>.

Appendices

Appendix 1 – Search Strategies

The Cochrane Library Search Description

Includes the following databases: Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment Database, NHS Economic Evaluation Database, and About The Cochrane Collaboration (Cochrane Groups).

Date & Time

June 20, 2012 at 4pm-5pm

Search

1. "Cannabis" OR "Marijuana" (1278)
2. "Anxiety Disorder" OR "Anxiety Disorders" (3364)
3. (#1) OR (#2) (28)

Total articles identified in Cochrane search = 28

Ovid MEDLINE® Search Description

Date & Time

June 20 9am – 2pm

Limits

English

Human

Mesh Terms

Note: **automatic explosion (explode)** - In PubMed, MeSH (Medical Subject Headings) terms (as well as any subheading that is the top of a "subheading tree") are "exploded" automatically to retrieve citations that carry the specified MeSH heading (or subheading)

and also retrieve citations that carry any of the more specific MeSH headings (or subheadings) indented beneath it in the Tree structure.

1. Anxiety Disorders
2. Cannabis
3. Marijuana Abuse
4. Marijuana Smoking
5. Cannabinoids

Anxiety Disorder

Tree Number(s): F03.080

Entry Terms:

- Anxiety Disorder
- Disorder, Anxiety
- Disorders, Anxiety
- Neuroses, Anxiety
- Anxiety Neuroses
- Anxiety States, Neurotic
- Anxiety State, Neurotic
- Neurotic Anxiety State
- Neurotic Anxiety States
- State, Neurotic Anxiety
- States, Neurotic Anxiety

See Also:

- Anxiety
 - Anti-Anxiety Agents
- All MeSH Categories

Psychiatry and Psychology Category
Mental Disorders

Anxiety Disorders

Agoraphobia
Neurocirculatory Asthenia
Obsessive-Compulsive Disorder
 Obsessive Hoarding
Panic Disorder
Phobic Disorders
Stress Disorders, Traumatic
 Combat Disorders
 Stress Disorders, Post-Traumatic
 Stress Disorders, Traumatic, Acute

Cannabis

Tree Number(s): B01.650.940.800.575.100.175.500

Entry Terms:

- Cannabi
- Hemp Plant
- Hemp Plants

- Plant, Hemp
- Plants, Hemp
- Cannabis indica
- Cannabis indicas
- indica, Cannabis
- indicas, Cannabis
- Marihuana
- Marihuanas
- Marijuana
- Marianuanas
- Ganja
- Ganjas
- Hashish
- Hashishs
- Hemp
- Hemps
- Bhang
- Bhangs
- Cannabis sativa
- Cannabis sativas
- sativa, Cannabis
- sativas, Cannabis

See Also:

- Cannabinoids
 - Marijuana Abuse
 - Marijuana Smoking
- All MeSH Categories
Organisms Category

Eukaryota

Plants

Viridiplantae

Streptophyta

Embryophyta

Angiosperms

Cannabaceae

Cannabis

Marijuana Abuse

Tree Number(s): C25.635, F03.900.635

Entry Terms:

- Abuse, Marijuana
- Marihuana Abuse
- Abuse, Marihuana
- Hashish Abuse
- Abuse, Hashish
- Cannabis-Related Disorder
- Cannabis Related Disorder
- Disorder, Cannabis-Related

- Cannabis Abuse
- Abuse, Cannabis
- Cannabis Dependence
- Dependence, Cannabis
- Marijuana Dependence
- Dependence, Marijuana

Previous Indexing:

- Cannabis (1966-1980)
 - Substance Abuse (1968-1980)
- All MeSH Categories
Diseases Category
Substance-Related Disorders
Marijuana Abuse
- All MeSH Categories
Psychiatry and Psychology Category
Mental Disorders
Substance-Related Disorders
Marijuana Abuse

Marijuana Smoking

Tree Number(s): F01.145.466.753.488

Entry Terms:

- Smoking, Marijuana
- Marihuana Smoking
- Smoking, Marihuana
- Cannabis Smoking
- Smoking, Cannabis
- Hashish Smoking
- Smoking, Hashish

Previous Indexing:

- Cannabis (1966-1987)
- All MeSH Categories
Psychiatry and Psychology Category
Behavior and Behavior Mechanisms
Behavior
Habits
Smoking
Marijuana Smoking

Cannabinoids

Tree Number(s): D02.455.849.090

Previous Indexing:

- Cannabis (1966-1976)

See Also:

- Receptors, Cannabinoid
 - Endocannabinoids
- All MeSH Categories
Chemicals and Drugs Category

Organic Chemicals
 Hydrocarbons
 Terpenes
Cannabinoids
 Cannabidiol
 Cannabinol
 Tetrahydrocannabinol

Search Entry	All results	English & Human Results
1. "Anxiety Disorders/therapy"[MH]	22629	19180
2. "Cannabis/therapeutic use"[MH]	1022	768
3. #1 & #2	3	3
4. "Marijuana Abuse" [MH]	3693	3266
5. #1 & #4	17	15
6. "Marijuana Smoking"[MH]	13	1896
7. #1 & #6	5	5
8. "Cannabinoids/therapeutic use"[MH]	2497	1554
9. #1 & #8	13	12
10. "Anxiety Disorders"[MH]	59266	49742
11. #10 & #4	81	71
12. #10 & #6	26	25
13. "Cannabis"[MH]	6297	3985
14. #10 & #13	21	16
15. "Cannabinoids"[MH]	9029	4205
16. #10 & #15	26	19
17. ("Anxiety Disorder"[TI]) OR "Anxiety Disorders"[TI]	4640	3787
18. "Cannabis"[TI]	3519	2225
19. #17 & #18	6	5
20. "Marijuana"[TI]	2709	2314
21. #17 & #20	3	2
22. "Marijuana Abuse"[TI]	28	22
23. #17 & #22	0	0
24. "Marijuana Smoking"[TI]	86	79
25. #17 & #24	0	0
26. "Cannabinoid"[TI]	4144	1470
27. #17 & #26	2	2
28. "Tetrahydrocannabinol"[TI]	2352	741
29. #17 & #28	0	0
30. "Anxiety Disorder" OR "Anxiety Disorders"	28651	22798
31. "Cannabis"	11281	7425

32. #30 & #31	120	98
33. "Marijuana"	17482	12561
34. #30 & #33	183	152
35. "Marijuana Abuse"	3748	3305
36. #30 & #35	72	64
37. "Marijuana Smoking"	2184	1994
38. #30 & #37	10	10
39. "Cannabinoid"	9446	3688
40. #30 & #39	42	16
41. "Tetrahydrocannabinol"	6437	2828
42. #30 & #41	11	6

Note: All articles were imported into RefWorks and checked for duplicates. A total of 521 articles were imported and 217 were unique.

Total articles identified in PubMed search = 217

PsycINFO/EBESCO Host Search Description

Date & Time

June 20, 2012 at 3pm-4pm

Search

1. DE "Anxiety Disorders" OR DE "Generalized Anxiety Disorder" (13217)
2. DE "Cannabis" OR DE "Marijuana" OR DE "Cannabinoids" (5974)
3. S1 AND S2 (30)

Total articles identified in PsycINFO = 30

References Hand Search

After reviewing the articles, we identified the following articles from our highest rated articles.

Gray Literature Search

Google Scholar for articles with all of the words " " AND cannabis = About # results (0.00 sec). The strategy for the gray literature search was to skim the titles of the articles. If an article seemed to address the benefit or harm of cannabis use among people with anxiety disorders then it would be read and examined. We only found articles that had already been identified through the previous searches.

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Appendix 2 – GRADE Methodology

Study Design	Quality of Evidence	Lower if	Higher if
Randomized trial →	High	Risk of bias -1 Serious -2 Very serious	Large effect +1 Large +2 Very Large
	Moderate	Inconsistency -1 Serious -2 Very serious	Dose response +1 Evidence of a gradient
Observational study →	Low	Indirectness -1 Serious -2 Very serious	All plausible confounding +1 Would reduce a demonstrated effect or
	Very Low	Imprecision -1 Serious -2 Very serious	+1 Would suggest a spurious effect when results show no effect
		Publication bias -1 Likely -2 Very likely	

Reference: Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. introduction- GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011 Apr;64(4):383-94.

Appendix 3 – Articles reviewed but excluded

Table 3		
Citation	Type of Study	Reason for Exclusion
Baker AL, Hides L, Lubman DI. Treatment of cannabis use among people with psychotic or depressive disorders: A systematic review. <i>J Clin Psychiatry</i> . 2010 Mar;71(3):247-54.	Systematic review	Did not deal with marijuana and anxiety. Focused on psychosis and depression.
Bonn-Miller MO, Zvolensky MJ. Marijuana use, abuse, and dependence: Evaluation of panic responsivity to biological challenge. <i>J Psychoactive Drugs</i> . 2009 Dec;41(4):331-6.	Laboratory Experiment, exposure to CO ₂ .	Exposure was to carbon dioxide and self reported panic and anxiety symptoms.
Bonn-Miller MO, Zvolensky MJ, Marshall EC, Bernstein A. Incremental validity of anxiety sensitivity in relation to marijuana withdrawal symptoms. <i>Addict Behav</i> . 2007 Sep;32(9):1843-51.	Cross sectional	Looked only at marijuana withdrawal.
Bricker JB, Russo J, Stein MB, Sherbourne C, Craske M, Schraufnagel TJ, et al. Does occasional cannabis use impact anxiety and depression treatment outcomes?: Results from a randomized effectiveness trial. <i>Depress Anxiety</i> . 2007;24(6):392-8.	Controlled clinical trial.	Studied the effect of CBT vs usual care and the effects of marijuana use on the outcomes. Studied panic attacks and depression treatment.
Buckner JD, Turner RJ. Social anxiety disorder as a risk factor for alcohol use disorders: A prospective examination of parental and peer influences. <i>Drug Alcohol Depend</i> . 2009 Feb 1;100(1-2):128-37.	Longitudinal cohort	Studied alcohol abuse.
Buckner JD, Heimberg RG, Schmidt NB. Social anxiety and marijuana-related problems: The role of social avoidance. <i>Addict Behav</i> . 2011 Jan-Feb;36(1-2):129-32.	Cross sectional study of 102 college students who were marijuana users and received college credit for participating.	Low quality Biased sample, small numbers. Some confounders were controlled for. Validated instruments used for data collection and classification.
Comeau N, Stewart SH, Loba P. The relations of trait anxiety, anxiety sensitivity, and sensation seeking to adolescents' motivations for alcohol, cigarette, and marijuana use. <i>Addict Behav</i> . 2001 Nov-Dec;26(6):803-25.	Cross sectional	Not an adult sample. Mean age 15.1 years (S.D. 1.9 years).
Dannon PN, Lowengrub K, Amiaz R, Grunhaus L, Kotler M. Comorbid cannabis use and panic disorder: Short term and long term follow-up study. <i>Hum Psychopharmacol</i> . 2004 Mar;19(2):97-101.	Cohort study	Did not deal with cannabis and anxiety. Focused on panic attacks.
Deas D, Gerding L, Hazy J. Marijuana and panic disorder. <i>J Am Acad Child Adolesc Psychiatry</i> . 2000 Dec;39(12):1467.	Editorial	Editorial
Degenhardt L, Hall W, Lynskey M. 'Alcohol, cannabis and tobacco use among australians: A comparison of their associations with other drug use and use disorders, affective and anxiety disorders, and psychosis': Reply. <i>Addiction</i> . 2001 12;96(12):1862-3.	Editorial	Letter to the editor in response to Fergusson (below).
Fergusson DM. 'Alcohol, cannabis and tobacco use among australians: A comparison of their associations with other drug use and use disorders, affective and anxiety disorders, and psychosis': Comment. <i>Addiction</i> . 2001 12;96(12):1861-2.	Editorial	Letter to the editor in response to Degenhart et al, 2001 (included in Table 1).
Frojd S, Ranta K, Kaltiala-Heino R, Marttunen M. Associations of social phobia and general anxiety with alcohol and drug use in a community sample of adolescents. <i>Alcohol Alcohol</i> . 2011 Mar-Apr;46(2):192-9.	Cohort study	Not an adult sample. Mean age 15.5 (S.D. 0.39).
Ganz VP, Volkmar F. Adverse reactions to marijuana use among college students. <i>J Am Coll Health Assoc</i> . 1976 Dec;25(2):93-6.	Case report	Five cases are described and discussed.
Hayatbakhsh MR, Najman JM, Jamrozik K, Mamun AA, Alati R, Bor W. Cannabis and anxiety and depression in young adults: A large prospective	Cohort study	Study of adolescents.

study. <i>J Am Acad Child Adolesc Psychiatry.</i> 2007 Mar;46(3):408		
Hill MN, Gorzalka BB. The endocannabinoid system and the treatment of mood and anxiety disorders. <i>CNS Neurol Disord Drug Targets.</i> 2009 Dec;8(6):451-8.	Systematic review	Biochemical summary - Summarizes current knowledge of the role of the endocannabinoid system in the etiology and treatment of mood and anxiety disorder.
Kelly TM, Daley DC, Douaihy AB. Treatment of substance abusing patients with comorbid psychiatric disorders. <i>Addict Behav.</i> 2012 Jan;37(1):11-24.	Evidence based review	Did not address cannabis use and anxiety disorders. CUD and bipolar disorder, depression and psychosis were discussed in detail.
Low NC, Lee SS, Johnson JG, Williams JB, Harris ES. The association between anxiety and alcohol versus cannabis abuse disorders among adolescents in primary care settings. <i>Fam Pract.</i> 2008 Oct;25(5):321-7.	Cross sectional	Sample was not adult. The subjects were 13 and 19 years of age (mean = 16.1, S.D. 1.24).
Lynskey MT. Life-time cannabis use and late onset mood and anxiety disorders. <i>Addiction.</i> 2007 Aug;102(8):1181-2.	Editorial	Editorial
Marmorstein NR, White HR, Loeber R, Stouthamer-Loeber M. Anxiety as a predictor of age at first use of substances and progression to substance use problems among boys. <i>J Abnorm Child Psychol.</i> 2010 Feb;38(2):211-24.	Cohort study	Not an adult sample. Assessed boys from first grade through high school.
Monshouwer K, VAN Dorsselaer S, Verdurmen J, Bogt TT, DE Graaf R, Vollebergh W. Cannabis use and mental health in secondary school children. findings from a dutch survey. <i>Br J Psychiatry.</i> 2006 Feb;188:148-53.	Cross sectional	Not an adult sample. Dutch students were between the ages of 12-16.
Neighbors B, Kempton T, Forehand R. Co-occurrence of substance abuse with conduct, anxiety, and depression disorders in juvenile delinquents. <i>Addict Behav.</i> 1992;17(4):379-86.	Cross sectional	Not an adult sample. The age range was 12 years, 7 months to 18 years, 7 months (mean = 15 years, 11 months).
Parslow R, Morgan AJ, Allen NB, Jorm AF, O'Donnell CP, Purcell R. Effectiveness of complementary and self-help treatments for anxiety in children and adolescents. <i>Med J Aust.</i> 2008 Mar 17;188(6):355-9.	Systematic review	Not an adult sample. The studies were included if the mean age was 19 years of age or younger.
Patton GC, Coffey C, Carlin JB, Degenhardt L, Lynskey M, Hall W. Cannabis use and mental health in young people: Cohort study. <i>BMJ.</i> 2002 Nov 23;325(7374):1195	cohort	Dtudy of adolescents
Roberts RE, Roberts CR, Xing Y. Comorbidity of substance use disorders and other psychiatric disorders among adolescents: Evidence from an epidemiologic survey. <i>Drug Alcohol Depend.</i> 2007 Apr;88 Suppl 1:S4-13.	Cohort study	Not an adult sample. Sample was aged 11-17 years of age.
Seibyl JP, Krystal JH, Charney DS. Marijuana (cannabis) use is anecdotally said to precipitate anxiety symptoms in patients with panic disorder. is there any research evidence to support this? also, can marijuana use precipitate or expose paranoia in patients with an underlying bipolar disorder? <i>J Clin Psychopharmacol.</i> 1990 Feb;10(1):78.	Opinion	Opinion
Strohle A, Muller M, Rupprecht R. Marijuana precipitation of panic disorder with agoraphobia. <i>Acta Psychiatr Scand.</i> 1998 Sep;98(3):254-5	Case Report	Case Report
Tambaro S, Bortolato M. Cannabinoid-related agents in the treatment of anxiety disorders: Current knowledge and future perspectives. <i>Recent Pat CNS Drug Discov.</i> 2012 Apr 1;7(1):25-40.	Review of biochemical pathways	Does not address key questions.
Zvolensky MJ, Bonn-Miller MO, Bernstein A, McLeish AC, Feldner MT, Leen-Feldner EW. Anxiety sensitivity interacts with marijuana use in the prediction of anxiety symptoms and panic-related catastrophic thinking among daily tobacco users. <i>Behav Res Ther.</i> 2006 Jul;44(7):907-24.	Cross sectional study	The study was focused on regular users of marijuana who also were regular tobacco users
Zvolensky MJ, Lewinsohn P, Bernstein A, Schmidt NB, Buckner JD, Seeley J, et al. Prospective associations between cannabis use, abuse, and dependence and panic attacks and disorder. <i>J Psychiatr Res.</i> 2008 Oct;42(12):1017-23.	Longitudinal cohort study	Did not deal with cannabis and anxiety. Focused on panic attacks.
Zvolensky MJ, Cogle JR, Johnson KA, Bonn-Miller MO, Bernstein A. Marijuana use and panic psychopathology among a representative sample of adults. <i>Exp</i>	Cohort Study	Did not deal with cannabis and anxiety. Focused on panic attacks.

Appendix 4 – Treatment Guideline

Guideline Title: Generalized anxiety disorder and panic disorder (with or without agoraphobia) in adults. Management in primary, secondary and community care.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Collaborating Centre for Mental Health on behalf of the National Institute for Health and Clinical Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Recommendations are marked **[2004]**, **[2004, amended 2011]** or **[new 2011]**. **[2004]** indicates that the evidence has not been updated and reviewed since 2004. **[2004, amended 2011]** indicates that the evidence has not been updated and reviewed since 2004 but a small amendment has been made to the recommendation. **[new 2011]** indicates that the evidence has been reviewed and the recommendation has been updated or added.

Principles of Care for People with Generalised Anxiety Disorder (GAD)

Information and Support for People with GAD, Their Families, and Careers

When working with people with GAD:

- Build a relationship and work in an open, engaging, and non-judgemental manner.
- Explore the person's worries in order to jointly understand the impact of GAD.
- Explore treatment options collaboratively with the person, indicating that decision making is a shared process.
- Ensure that discussion takes place in settings in which confidentiality, privacy, and dignity are respected. **[new 2011]**

When working with people with GAD:

- Provide information appropriate to the person's level of understanding about the nature of GAD and the range of treatments available.
- If possible, ensure that comprehensive written information is available in the person's preferred language and in audio format.
- Offer independent interpreters if needed. **[new 2011]**

When families and carers are involved in supporting a person with GAD, consider:

- Offering a carer's assessment of their caring, physical, and mental health needs.
- Providing information, including contact details, about family and carer support groups and voluntary organisations, and helping families or carers to access these.
- Negotiating between the person with GAD and their family or carers about confidentiality and the sharing of information.
- Providing written and verbal information on GAD and its management, including how families and carers can support the person.
- Providing contact numbers and information about what to do and who to contact in a crisis. **[new 2011]**

Inform people with GAD about local and national self-help organisations and support groups, in particular where they can talk to others with similar experiences. **[new 2011]**

For people with GAD who have a mild learning disability or mild acquired cognitive impairment, offer the same interventions as for other people with GAD, adjusting the method of delivery or duration of the intervention if necessary to take account of the disability or impairment. **[new 2011]**

When assessing or offering an intervention to people with GAD and a moderate to severe learning disability or moderate to severe acquired cognitive impairment, consider consulting with a relevant specialist. **[new 2011]**

Stepped Care for People with GAD

A stepped-care model (see figure in chapter 1, section 1.2 of the short version of the original guideline document) is used to organise the provision of services and to help people with GAD, their families, carers, and practitioners to choose the most effective interventions.

Follow the stepped-care model, offering the least intrusive, most effective intervention first. **[new 2011]**

Step 1: All Known and Suspected Presentations of GAD

Identification

Identify and communicate the diagnosis of GAD as early as possible to help people understand the disorder and start effective treatment promptly. **[new 2011]**

Consider the diagnosis of GAD in people presenting with anxiety or significant worry, and in people who attend primary care frequently who:

- Have a chronic physical health problem **or**
- Do not have a physical health problem but are seeking reassurance about somatic symptoms (particularly older people and people from minority ethnic groups) **or**
- Are repeatedly worrying about a wide range of different issues **[new 2011]**

When a person with known or suspected GAD attends primary care seeking reassurance about a chronic physical health problem or somatic symptoms and/or repeated worrying, consider with the person whether some of their symptoms may be due to GAD. **[new 2011]**

Assessment and Education

For people who may have GAD, conduct a comprehensive assessment that does not rely solely on the number, severity, and duration of symptoms, but also considers the degree of distress and functional impairment. **[new 2011]**

As part of the comprehensive assessment, consider how the following factors might have affected the development, course, and severity of the person's GAD:

- Any comorbid depressive disorder or other anxiety disorder
- Any comorbid substance misuse
- Any comorbid medical condition
- A history of mental health disorders
- Past experience of, and response to, treatments **[new 2011]**

For people with GAD and a comorbid depressive or other anxiety disorder, treat the primary disorder first (that is, the one that is more severe and in which it is more likely that treatment will improve overall functioning). **[new 2011]** (For National Institute for Health and Clinical Excellence [NICE] guidance on depression, obsessive-compulsive disorder, and post-traumatic stress disorder see section 6 of the short version of the original guideline document. NICE is developing a guideline on identification and pathways to care for common mental health disorders. Publication expected Summer 2011.)

For people with GAD who misuse substances, be aware that:

- Substance misuse can be a complication of GAD.
- Non-harmful substance use should not be a contraindication to the treatment of GAD.
- Harmful and dependent substance misuse should be treated first as this may lead to significant improvement in the symptoms of GAD. **[new 2011]** (For NICE guidance on drug misuse and alcohol-use disorder see section 6 of the short version of the original guideline document. NICE is developing a guideline on the diagnosis and management of alcohol dependence and harmful alcohol use in young people and adults. Publication expected February 2011.)

Following assessment and diagnosis of GAD:

- Provide education about the nature of GAD and the options for treatment, including the 'Understanding NICE guidance' booklet (see the "Patient Resources" field).
- Monitor the person's symptoms and functioning (known as active monitoring).

This is because education and active monitoring may improve less severe presentations and avoid the need for further interventions. **[new 2011]**

Discuss the use of over-the-counter medications and preparations with people with GAD. Explain the potential for interactions with other prescribed and over-the-counter medications and the lack of evidence to support their safe use. **[new 2011]**

Step 2: Diagnosed GAD That Has Not Improved after Step 1 Interventions

Low-intensity Psychological Interventions for GAD

For people with GAD whose symptoms have not improved after education and active monitoring in step 1, offer one or more of the following as a first-line intervention, guided by the person's preference:

- Individual non-facilitated self-help
- Individual guided self-help
- Psychoeducational groups **[new 2011]**

Individual non-facilitated self-help for people with GAD should:

- Include written or electronic materials of a suitable reading age (or alternative media)
- Be based on the treatment principles of cognitive behavioural therapy (CBT)
- Include instructions for the person to work systematically through the materials over a period of at least 6 weeks
- Usually involve minimal therapist contact, for example an occasional short telephone call of no more than 5 minutes **[new 2011]**

Individual guided self-help for people with GAD should:

- Include written or electronic materials of a suitable reading age (or alternative media)
- Be supported by a trained practitioner, who facilitates the self-help programme and reviews progress and outcome
- Usually consist of five to seven weekly or fortnightly face-to-face or telephone sessions, each lasting 20–30 minutes **[new 2011]**

Psychoeducational groups for people with GAD should:

- Be based on CBT principles, have an interactive design and encourage observational learning
- Include presentations and self-help manuals
- Be conducted by trained practitioners
- Have a ratio of one therapist to about 12 participants
- Usually consist of six weekly sessions, each lasting 2 hours **[new 2011]**

Practitioners providing guided self-help and/or psychoeducational groups should:

- Receive regular high-quality supervision
- Use routine outcome measures and ensure that the person with GAD is involved in reviewing the efficacy of the treatment **[new 2011]**

Step 3: GAD with Marked Functional Impairment or That Has Not Improved after Step 2 Interventions

Treatment Options

For people with GAD and marked functional impairment, or those whose symptoms have not responded adequately to step 2 interventions:

- Offer either
 - An individual high-intensity psychological intervention (see recommendations below) **or**
 - Drug treatment (see recommendations below)
- Provide verbal and written information on the likely benefits and disadvantages of each mode of treatment, including the tendency of drug treatments to be associated with side effects and withdrawal syndromes.
- Base the choice of treatment on the person's preference as there is no evidence that either mode of treatment (individual high-intensity psychological intervention or drug treatment) is better. **[new 2011]**

High-Intensity Psychological Interventions

If a person with GAD chooses a high-intensity psychological intervention, offer either cognitive behavioral therapy (CBT) or applied relaxation. **[new 2011]**

CBT for people with GAD should:

- Be based on the treatment manuals used in the clinical trials of CBT for GAD
- Be delivered by trained and competent practitioners
- Usually consist of 12–15 weekly sessions (fewer if the person recovers sooner; more if clinically required), each lasting 1 hour **[new 2011]**

Applied relaxation for people with GAD should:

- Be based on the treatment manuals used in the clinical trials of applied relaxation for GAD
- Be delivered by trained and competent practitioners
- Usually consist of 12–15 weekly sessions (fewer if the person recovers sooner; more if clinically required), each lasting 1 hour **[new 2011]**

Practitioners providing high-intensity psychological interventions for GAD should:

- Have regular supervision to monitor fidelity to the treatment model, using audio or video recording of treatment sessions if possible and if the person consents
- Use routine outcome measures and ensure that the person with GAD is involved in reviewing the efficacy of the treatment **[new 2011]**

Consider providing all interventions in the preferred language of the person with GAD if possible. **[new 2011]**

Drug Treatment

If a person with GAD chooses drug treatment, offer a selective serotonin reuptake inhibitor (SSRI). Consider offering sertraline first because it is the most cost-effective drug, but note that at the time of publication (January 2011) sertraline did not have UK marketing authorisation for this indication. Informed consent should be obtained and documented. Monitor the person carefully for adverse reactions. **[new 2011]**

If sertraline is ineffective, offer an alternative SSRI or a serotonin–noradrenaline reuptake inhibitor (SNRI), taking into account the following factors:

- Tendency to produce a withdrawal syndrome (especially with paroxetine and venlafaxine)
- The side-effect profile and the potential for drug interactions
- The risk of suicide and likelihood of toxicity in overdose (especially with venlafaxine)
- The person's prior experience of treatment with individual drugs (particularly adherence, effectiveness, side effects, experience of withdrawal syndrome, and the person's preference) **[new 2011]**

If the person cannot tolerate SSRIs or SNRIs, consider offering pregabalin. **[new 2011]**

Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises. Follow the advice in the 'British national formulary' on the use of a benzodiazepine in this context. **[new 2011]**

Do not offer an antipsychotic for the treatment of GAD in primary care. **[new 2011]**

Before prescribing any medication, discuss the treatment options and any concerns the person with GAD has about taking medication. Explain fully the reasons for prescribing and provide written and verbal information on:

- The likely benefits of different treatments
- The different propensities of each drug for side effects, withdrawal syndromes, and drug interactions
- The risk of activation with SSRIs and SNRIs, with symptoms such as increased anxiety, agitation and problems sleeping
- The gradual development, over 1 week or more, of the full anxiolytic effect
- The importance of taking medication as prescribed and the need to continue treatment after remission to avoid relapse **[new 2011]**

Take into account the increased risk of bleeding associated with SSRIs, particularly for older people or people taking other drugs that can damage the gastrointestinal mucosa or interfere with clotting (for example, non-steroidal anti-inflammatory drugs [NSAIDs] or aspirin). Consider prescribing a gastroprotective drug in these circumstances. **[new 2011]**

For people aged under 30 who are offered an SSRI or SNRI:

- Warn them that these drugs are associated with an increased risk of suicidal thinking and self-harm in a minority of people under 30 **and**
- See them within 1 week of first prescribing **and**
- Monitor the risk of suicidal thinking and self-harm weekly for the first month **[new 2011]**

For people who develop side effects soon after starting drug treatment, provide information and consider one of the following strategies:

- Monitoring the person's symptoms closely (if the side effects are mild and acceptable to the person) **or**
- Reducing the dose of the drug **or**
- Stopping the drug and, according to the person's preference, offering either
 - An alternative drug (see recommendations above) **or**
 - A high-intensity psychological intervention (see recommendations above) **[new 2011]**

Review the effectiveness and side effects of the drug every 2–4 weeks during the first 3 months of treatment and every 3 months thereafter. **[new 2011]**

If the drug is effective, advise the person to continue taking it for at least a year as the likelihood of relapse is high. **[new 2011]**

Inadequate Response to Step 3 Interventions

If a person's GAD has not responded to a full course of a high-intensity psychological intervention, offer a drug treatment (see recommendations above). **[new 2011]**

If a person's GAD has not responded to drug treatment, offer either a high-intensity psychological intervention (see recommendations above) or an alternative drug treatment (see recommendations above). **[new 2011]**

If a person's GAD has partially responded to drug treatment, consider offering a high-intensity psychological intervention in addition to drug treatment. **[new 2011]**

Consider referral to step 4 if the person with GAD has severe anxiety with marked functional impairment in conjunction with:

- A risk of self-harm or suicide **or**
- Significant comorbidity, such as substance misuse, personality disorder or complex physical health problems **or**
- Self-neglect **or**
- An inadequate response to step 3 interventions **[new 2011]**

Step 4: Complex, Treatment-Refractory GAD and Very Marked Functional Impairment or High Risk of Self-Harm (Step 4 normally refers to community mental health teams but may include specialist services and specialist practitioners in primary care.)

Assessment

Offer the person with GAD a specialist assessment of needs and risks, including:

- Duration and severity of symptoms, functional impairment, comorbidities, risk to self, and self-neglect
- A formal review of current and past treatments, including adherence to previously prescribed drug treatments and the fidelity of prior psychological interventions, and their impact on symptoms and functional impairment
- Home environment
- Support in the community
- Relationships with and impact on families and carers **[new 2011]**

Review the needs of families and carers and offer an assessment of their caring, physical, and mental health needs if one has not been offered previously. **[new 2011]**

Develop a comprehensive care plan in collaboration with the person with GAD that addresses needs, risks, and functional impairment and has a clear treatment plan. **[new 2011]**

Treatment

Inform people with GAD who have not been offered or have refused the interventions in steps 1–3 about the potential benefits of these interventions, and offer them any they have not tried. **[new 2011]**

Consider offering combinations of psychological and drug treatments, combinations of antidepressants, or augmentation of antidepressants with other drugs, but exercise caution and be aware that:

- Evidence for the effectiveness of combination treatments is lacking **and**
- Side effects and interactions are more likely when combining and augmenting antidepressants **[new 2011]**

Combination treatments should be undertaken only by practitioners with expertise in the psychological and drug treatment of complex, treatment-refractory anxiety disorders and after full discussion with the person about the likely advantages and disadvantages of the treatments suggested. **[new 2011]**

When treating people with complex and treatment-refractory GAD, inform them of relevant clinical research in which they may wish to participate, working within local and national ethical guidelines at all times. **[new 2011]**