

Clinical Policy: Concomitant Antidepressant Treatment

Reference Number: AZ.CP.PHAR.10.11.11

Effective Date: 07.16

Last Review Date: 07.18

Line of Business: Medicaid Arizona

Revision Log

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

Description

Concomitant use of more than one antidepressant to include the following:

1. Two SSRIs
2. An SSRI in combination with an SNRI
3. Two SNRIs

FDA approved indication

Treatment Resistant Depression

Obsessive Compulsive Disorder (clomipramine with fluvoxamine)

Limitation of use:

- Cross tapers will automatically be approved for 60 days. Providers must submit a prior authorization request for continued utilization of concomitant use of any 2 antidepressants beyond the 60 days allowed for cross tapering.
- Excluded from this policy are TCA's, trazadone, mirtazapine, bupropion which are often used as adjunctive therapy with other agents including other antidepressants.
- Excluded from this policy is doxepin.

Policy/Criteria

Provider must submit documentation (including office chart notes and lab results) supporting that member has met all approval criteria.

Provider must provide supporting documentation that adherence to the treatment regimen has not been a contributing factor to the lack of response in the medication trial.

It is the policy of health plans affiliated with Centene Corporation[®] that concomitant use of more than one antidepressant is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. FDA approved diagnosis for use of antidepressant (must meet all):

1. Diagnosis of treatment resistant depression
2. Evidence of adequate trials of at least three (3) individual antidepressants listed on the AHCCCS Behavioral Health Drug Lists, from at least two(2) different therapeutic classes for 4-6 weeks at maximum tolerated doses and
3. Failure to previous trials of single agent antidepressants is due to:
 - a. Inadequate response to maximum tolerated dose

CLINICAL POLICY

Concomitant Antidepressant Treatment

- b. Adverse reaction(s)
OR
- c. Break through symptoms
- 4. Appropriate clinical monitoring of target symptoms, adverse reactions including but not limited to signs and symptoms of serotonin syndrome, adherence to treatment, suicide risk, heart rate, blood pressure and weight has been completed

Approval duration: 6 months

B. Obsessive Compulsive Disorder

- 1. Diagnosis of obsessive compulsive disorder
- 2. Evidence of adequate trials of at least three (3) individual antidepressants listed on the AHCCCS Behavioral Health Drug Lists, from at least two (2) different therapeutic classes for 4-6 weeks at maximum tolerated doses and
AND
- 3. Failure to previous trials of single agent antidepressants is due to:
 - a. Inadequate response to maximum tolerated dose
 - b. Adverse reaction(s)
OR
 - c. Break through symptoms
- 4. Appropriate clinical monitoring of target symptoms, adverse reactions including but not limited to signs and symptoms of serotonin syndrome, adherence to treatment, suicide risk, heart rate, blood pressure and weight has been completed

Approval duration: 6 months

C. Other diagnoses/indications

- 1. Refer to CRP.PMN.53 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized)

II. Continued Therapy

- A. Currently receiving medication via a health plan affiliated with Centene Corporation or member has previously met initial approval criteria;
- B. Documentation of positive response to therapy (sign/symptom reduction, etc.)

Approval duration: 12 months

III. Diagnoses/Indications for which coverage is NOT authorized:

- A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – CP.PMD.53 or evidence of coverage documents
- B. Members currently taking an MAOI medication.
- C. Members with significant polypharmacy or concomitant psychiatric/medical comorbidities that have a potential for adverse effects.

CLINICAL POLICY

Concomitant Antidepressant Treatment

- D. Members on medication combinations, doses, or for identified indications that do not meet published practice guidelines or treatment protocols.
- E. Members on medication regimens that do not have adequate safeguards or monitoring to ensure safety and reasonable expectation of response to regimen

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ECG (EKG): Electrocardiogram

MAOI: Monoamine Oxidase Inhibitors (e.g. Nardil, Parnate, Eldepryl, Marplan)

Serotonin Syndrome: condition that occurs when medications cause high levels of serotonin. Symptoms can range from mild (shivering, diarrhea) to severe (muscle rigidity, fever, seizures) Can be fatal if not treated.

SSRI: Selective Serotonin Reuptake Inhibitor

SNRI: Serotonin-Norepinephrine Reuptake Inhibitor

TCA: Tricyclic Antidepressant

QTc: In electrocardiography, QT interval is the measure of time between the onset of ventricular depolarization (Q wave) and completion of ventricular repolarization (T wave).

Appendix B: General Information

- Avoid TCA use in patients with cardiac instability.
- QTc prolongation is a well established marker of risk for Torsades de Pointes (TdP). TdP is a ventricular arrhythmia that can be fatal. Clinicians should make a careful analysis of other QTc risk factors when prescribing psychiatric medications.
- Escitalopram and citalopram are agents with known risk of QTc prolongation
- Clomipramine, Desipramine, Imipramine, nortriptyline, trimipramine and mirtazapine have potential risks of QTc prolongation.
- Appropriate clinical monitoring for TCAs (if being prescribed) would include but is not limited to, TCA levels and/or an ECG (EKG) at baseline and follow up
- The combination of clomipramine (TCA) with fluvoxamine (SSRI) is considered standard of care for obsessive compulsive disorder.

Appendix C: Therapeutic Alternatives

N/A

V. Dosage and Administration*

**Only Preferred or formulary antidepressants listed.*

Drug Name	Class	Maximum Dose
Citalopram (Celexa)	SSRI	Adults: 40mg/day Geriatrics: 20mg/day Adolescents & Children 40mg/day
Escitalopram (Lexapro)	SSRI	Adults: 20mg/day Geriatric: 10mg/day Adolescents & Children 20mg/day

CLINICAL POLICY

Concomitant Antidepressant Treatment

Fluoxetine (Prozac)	SSRI	Adults: 80mg/day; 90mg/week PO weekly formulation (PA required for weekly) Adolescent & Children: 60mg/day Children 2-3 years old: 0.5mg/kg/day up to 40mg
Fluvoxamine (Luvox, Luvox CR)	SSRI	Adults: 300mg/day Adolescents: 300mg/day Children: 200-250mg/day
Paroxetine (Paxil, Paxil CR)	SSRI	Adults: 60mg/day IR 75mg/day CR Geriatric: 40mg/day IR 50mg/day CR Adolescents: 50mg/day Children 7-12 years old: 50mg/day
Sertraline (Zoloft)	SSRI	200mg/day
Viibryd (vilazodone)	SSRI PA Required	Adults: 40mg/day
Desvenlafaxine(Pristiq)	SNRI	Adults: 400mg/day
Duloxetine (Cymbalta)	SNRI	120mg/day
Venlafaxine(Effexor, Effexor ER)	SNRI	IR & ER: 225mg/day
Amitriptyline(Elavil)	TCA	150mg/day outpatients; 300mg/day hospitalized patients
Amoxapine (Asendin)	TCA	Adults: 400mg/day outpatients; 600mg/day hospitalized patients Elderly: 300mg/day Adolescents: 400mg/day
Clomipramine (Anafranil)	TCA	Adults: 250mg/day Adolescents: 3mg/kg/day up to 200mg/day
Desipramine(Norpramin)	TCA	Adults: 200mg/day outpatient; 300mg/day hospitalized patients. Elderly and Adolescents: 150mg/day
Doxepin (Sinequin)	TCA	Adults: 300mg/day Adolescents: 3mg/kg/day up to 100mg/day
Imipramine (Tofranil)	TCA	Adults: 200mg/day outpatients; 300mg/day hospitalized patients. Adolescents: 100mg/day Children: 2.5mg/kg/day not to exceed 50mg for < 12 years of age or 75mg/day > 12

CLINICAL POLICY

Concomitant Antidepressant Treatment

		years of age
Nortriptyline (Pamelor)	TCA	Adults: 150mg/day Elderly and Adolescents: 50mg/day
Protriptyline (Vivactil)	TCA	Adults: 60mg/day Elderly and Adolescents: 30mg/day
Trimipramine	TCA	Adults: 200mg/day outpatients; 300mg/day hospitalized patients. Elderly and Adolescents: 100mg

VI. Product Availability

Drug	Availability
Citalopram (Celexa)	Oral Solution: 10mg/5 ml Tablets: 10, 20, 40 mg
Escitalopram (Lexapro)	Oral Solution: 5mg/5ml Tablets: 5, 10, 20 mg
Fluoxetine (Prozac) Prozac weekly requires a PA	Oral solution: 20mg/5ml Tablets:10, 20, 40, 60 mg. Tabs are Non-Formulary Capsules: 10, 20, 40 mg Weekly Capsules: 90mg delayed release
Fluvoxamine (Luvox, Luvox CR)	ER Capsules: 100, 150mg Tablets:25, 50, 100 mg
Paroxetine (Paxil, Paxil CR)	Oral Suspension: 10mg/5ml ER Tablets: 12.5, 25, 37.5 mg Tablets: 10, 20, 30, 40 mg
Sertraline (Zoloft)	Oral solution: 20mg/ml Tablets: 25, 50, 100 mg
Viibryd (vilazodone)	Tablet: 10, 20 40mg Tablet Starter Kit: 10 & 20mg
Desvenlafaxine(Pristiq)	Tablet ER: 50, 100mg Tablet ER (succinate): 25, 50, 100mg
Duloxetine (Cymbalta)	Capsules: 20, 30, 40, 60
Venlafaxine(Effexor, Effexor ER)	Capsule ER: 37.5, 75, 150 mg Tablet IR: 25, 37.5, 50, 75, 100 mg Tablet ER: 37.5, 75, 150, 225mg (Non-formulary)
Amitriptyline(Elavil)	Tablet: 10, 25, 50, 75, 100, 150 mg
Amoxapine (Asendin)	Tablet: 25, 50, 100, 150mg
Clomipramine (Anafranil)	Capsule: 25, 50, 75 mg
Desipramine(Norpramin)	Tablets:10, 25, 50, 75, 100, 150 mg
Doxepin (Sinequin)	Capsule: 10,25,50, 75, 100, 150 Oral Solution: 10mg/ml

CLINICAL POLICY

Concomitant Antidepressant Treatment

Imipramine (Tofranil)	Tablet: 10, 25, 50 mg Capsules: 75,100, 150 mg
Nortriptyline (Pamelor)	Capsule:10, 25, 50, 75 Oral Solution: 10mg/5ml
Protriptyline (Vivactil)	Tablet: 5, 10mg
Trimipramine	Capsule: 25, 50, 100mg

VII. References

1. Cenpatico Integrated Care Provider Manual Section 3.8 (Behavioral Health Network provider Service Delivery Requirements-Psychotropic Medication: Prescribing and Monitoring 4/1/2018 edition
2. American Psychiatric Association Practice Guideline for the Treatment of patients with Major Depressive Disorder, 3rd edition. American Psychiatric Association; October 2010. Accessed April 2018
https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf
3. American Psychiatric Association Practice Guideline for the Treatment of Patients with Obsessive-compulsive Disorder (Guideline Watch march 2013)
https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/ocd-watch.pdf Accessed April 2018.
4. Rush AJ¹, Fava M, Wisniewski SR, Lavori PW, Sequenced Treatment Alternatives to Relieve Depression (STAR*D): Rationale and design
<https://www.ncbi.nlm.nih.gov/pubmed/15061154> Accessed April 2018
5. Rush AJ; Trivedi MH; Stewart JW; et al. Combining Medications to Enhance Depression Outcomes (CO-MED): Acute and Long-Term Outcomes of a Single-Blind Randomized Study. *Am J Psychiatry* 2011; 168:689-701.
6. Trivedi MH, Fava M, Wisniewski SR, et al. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med.* 2006;354(12):1243-52.
7. Debonnel G; Saint-Andre E; Hebert C; et al. Differential Physiological Effects of a Low Dose and High Doses of Venlafaxine in Major Depression. *Int J Neuropsychopharmacol.* 2007 Feb;10(1):51-61
8. *Clinical Pharmacology* [database online]. Tampa, FL: Gold Standard, Inc.; 2018. Available <http://www.clinicalpharmacology-ip.com/> Accessed April 2018
9. Brouillette J, Nattel S A Practical Approach to Avoiding Cardiovascular Adverse Effects of Psychoactive Medications. *Can J Psychiatry* 2017 Dec;33(12):1577-1586. doi: 10.1016/j.cjca.2017.09.001. Epub 2017 Sep 11
<https://www.ncbi.nlm.nih.gov/pubmed/29173600> Accessed April 2018
10. QT Prolongation, Torsades de Pointes, and Psychotropic Medications: A 5-Year Update *Psychosomatics.* 2018 Mar - Apr;59(2):105-122. doi: 10.1016/j.psym.2017.10.009. Epub 2017 Nov 3
<https://www.ncbi.nlm.nih.gov/pubmed/29275963>
11. CredibleMeds <https://www.crediblemeds.org/> Accessed April 2018

CLINICAL POLICY

Concomitant Antidepressant Treatment

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Converted to new template Added Dosage and Administration; Added Product availability; updated references; TCA's no longer reject as concomitant therapy;	03/2018	07/18

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

CLINICAL POLICY

Concomitant Antidepressant Treatment

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

©2017 Centene Corporation. All rights reserved. All materials are exclusively owned by Centene Corporation and are protected by United States copyright law and international copyright law. No part of this publication may be reproduced, copied, modified, distributed, displayed, stored in a retrieval system, transmitted in any form or by any means, or otherwise published without the prior written permission of Centene Corporation. You may not alter or remove any trademark, copyright or other notice contained herein. Centene® and Centene Corporation® are registered trademarks exclusively owned by Centene Corporation.