“I’m not [an alcoholic], my mother had me tested”: Is prazosin the next “Big Bang” in alcohol use disorder treatment?

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Objectives
1) Explain the epidemiology, risk factors, and diagnostic criteria for AUD
2) Compare current evidence-based AUD treatments and identify therapeutic limitations
3) Describe the complex pathophysiology of AUD and analyze primary literature evaluating use of prazosin as a novel therapeutic agent
4) Formulate an evidence-based recommendation regarding the use of prazosin as an alternative treatment for AUD

**Abbreviations used throughout handout defined in Appendix 1**
I. Alcohol Use Disorder

1) Background
   a) SDU: 0.6 fl oz of 100% alcohol

<table>
<thead>
<tr>
<th>Age</th>
<th>Number standard drinks</th>
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<tbody>
<tr>
<td>Men &lt; 65 years</td>
<td>≤ 4 daily, ≤ 14 weekly</td>
</tr>
<tr>
<td>Men &gt; 65 years</td>
<td>≤ 3 daily, ≤ 7 weekly</td>
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<tr>
<td>Women All ages</td>
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2) Definition
   a) Maladaptive pattern of alcohol misuse leading to clinically significant impairment or distress
   b) Chronic and relapsing SUD characterized by cognitive, behavioral, and physiological symptoms indicating compulsive alcohol use

3) Epidemiology
   a) Affects ~283 million individuals globally
      i) Alcohol use and AUD risk peak in younger adults
         (1) Average age of first drink ~15 years
         (2) Highest past-year drinking prevalence (82.6%) in individuals 21-25 years old
         (3) Highest AUD prevalence (10.7%) in individuals 18-25 years old
   b) $249 billion in estimated alcohol-related costs in the US in 2010
   c) US demographic disparities
      i) Men more likely to drink alcohol and receive AUD diagnosis than women
      ii) Native Americans (9.2%) > non-Hispanic whites (5.9%) > Blacks (5.6%) > Hispanics (5.1%)
         > Pacific Islanders (3.5%) > Asians (3.0%)
      iii) Never married > separated, divorced, or widowed > married or cohabiting

4) Etiology
   a) Multifactorial with various biological, psychological, and social factors
      i) Neurotransmitter or hypothalamic-pituitary-adrenal axis dysregulation
      ii) Prefrontal cortex dysfunction
      iii) Peer pressure
      iv) Psychological stressors
   b) Risk factors
      i) Coexisting psychiatric disorders and personality traits (impulsivity)
      ii) Demographics (see above)
      iii) Genetic predisposition (accounts for ~50% of AUD risk)
         (1) Aldehyde dehydrogenase family 2 receptors
         (2) GABA type A receptors
      iv) Environmental factors (account for ~50% of AUD risk)
         (1) Childhood and adolescent stressors: Verbal, physical, and sexual abuse
         (2) Household instability: Physical violence, parental psychiatric illness, substance exposure in youth, incarcerated or deceased family members

5) Monitoring parameters
   a) Ethyl glucuronide
      i) Ethanol metabolite in urine
      ii) Marker of alcohol consumption within 3-4 days
   b) GGT
      i) Enzyme that increases with long-term (weeks-months) heavy alcohol consumption
      ii) Normal < 51 IU/L
         (1) High sensitivity
         (2) False positives include obstructive liver disease or concurrent anticonvulsant use
c) Markers for alcohol-induced liver disease
   i) LFT
      (1) Increased AST
      (2) Increased ALT
   ii) Increased INR
   iii) Decreased prealbumin
6) Complications3,4,10,11
   a) Chronic AUD decreases lifespan by 10-15 years
      i) Alcohol use accounts for 9.8% of all US deaths and 5.9% of global deaths
      ii) Leading risk factor for premature death and disability
         (1) Cardiovascular disease and diabetes (33.4%)
         (2) Accidents/injuries (17.1%)
         (3) Gastrointestinal diseases (16.2%)
         (4) Hepatocellular and digestive system cancers (12.5%)
         (5) Suicide
   7) Standardized rating scales12-15
      a) Used to identify heavy alcohol use within 1 year, prompting further evaluation of AUD
      b) Validated screening methods recommended by US Preventive Services Task Force

<table>
<thead>
<tr>
<th>Table 2. Long-term AUD complications by body system3</th>
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</thead>
<tbody>
<tr>
<td><strong>Body system</strong></td>
</tr>
<tr>
<td>Cardiovascular</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Genitourinary/reproductive</td>
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<tr>
<td>Hematopoietic</td>
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<tr>
<td>Hepatic</td>
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<tr>
<td>Hormonal</td>
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<tr>
<td>Neurologic</td>
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<tr>
<td>Renal</td>
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<tr>
<td>Skeletal</td>
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<table>
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<tr>
<th>Table 3. Validated AUD screening tools12-15</th>
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<tbody>
<tr>
<td><strong>Intervention</strong></td>
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<tr>
<td>------------------</td>
</tr>
<tr>
<td>Score range</td>
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<tr>
<td>Positive screen</td>
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<tr>
<td>Sensitivity</td>
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<tr>
<td>Specificity</td>
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</tbody>
</table>
8) Diagnostic criteria\textsuperscript{2,5,16}
   a) Underdiagnosed with 1 in 6 US adults questioned about drinking behavior by health provider
   b) Diagnosis based on evaluation of 11 criteria within 12-month period
   c) DSM criteria
      i) DSM-IV categorized alcohol abuse and alcohol dependence as two distinct disorders
      ii) DSM-5 collectively categorizes alcohol abuse and alcohol dependence as alcohol use disorder with mild, moderate, and severe sub-classifications
      iii) DSM-5 eliminates legal problems, but adds craving as AUD criterion

9) Treatment\textsuperscript{3,4,17,18}
   a) Non-pharmacological interventions
      i) Psychosocial therapy (most common modality)
      ii) Self-help groups (Alcoholics Anonymous)
      iii) Cognitive behavioral therapy
      iv) Motivational enhancement therapy
      v) Contingency management
      vi) Cue exposure and relaxation training
      vii) Group or family therapy
b) Pharmacotherapy

i) Pharmacotherapy selection per 2018 APA guidelines

<table>
<thead>
<tr>
<th>Medication</th>
<th>FDA-approval</th>
<th>Strength of recommendation</th>
<th>Treatment goal</th>
<th>Place in therapy</th>
<th>Mechanism of action</th>
<th>Dosing</th>
<th>Contraindications</th>
<th>Monitoring</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naltrexone (Vivitrol®)</td>
<td>Yes (11/1984)</td>
<td>1B recommendation</td>
<td>Reduce alcohol consumption or achieve abstinence</td>
<td>Preference for pharmacotherapy or no response to non-pharmacological treatments</td>
<td>Pure opioid antagonist</td>
<td>Oral: 50-100 mg daily IM: 380 mg every 4 weeks to upper outer quadrant of gluteal area (REMS program)</td>
<td>Acute hepatitis or hepatic failure</td>
<td>-LFT and Scr at baseline -Repeat LFT at 6 months, annually</td>
<td>6-12 months at minimum</td>
</tr>
<tr>
<td>Acamprosate</td>
<td>Yes (07/2004)</td>
<td>1B recommendation</td>
<td>Achieve abstinence</td>
<td>Preferred for achieving abstinence</td>
<td>GABA agonist/glutamate antagonist</td>
<td>Normal: 666 mg TID with meals CrCl 30-50 mL/min: 333 mg TID with meals CrCl &lt; 30 mL/min: Contraindicated</td>
<td>Severe renal impairment -Avoid as first-line agent in mild to moderate renal impairment (dose reduction required)</td>
<td>-LFT and EKG at baseline -Repeat LFT at 1 month, 6 months, annually</td>
<td>Undetermined/lifelong</td>
</tr>
<tr>
<td>Disulfiram (Antabuse®)</td>
<td>Yes (12/1983)</td>
<td>2C suggestion</td>
<td>Reduce alcohol consumption or achieve abstinence</td>
<td>Preferred for maintaining abstinence *Abstinence required for initiation, but may continue therapy if relapse occurs</td>
<td>Aldehyde dehydrogenase inhibitor</td>
<td>Initial: Up to 500 mg daily for 1-2 weeks (max: 500 mg/day) Maintenance: 250 mg daily (range: 125-500 mg/day, max: 500 mg/day) *May not be given until patient abstained from alcohol ≥ 12 hours *Morning dosing preferred</td>
<td>Risk of disulfiram reaction (black box warning) with concurrent alcohol, metronidazole, paraldehyde, or alcohol-containing preparation use (cough syrup, tonic) -Psychosis -Severe myocardial disease or coronary occlusion</td>
<td>-LFT and EKG at baseline -Repeat LFT at 1 month, 6 months, annually</td>
<td>Undetermined/lifelong</td>
</tr>
<tr>
<td>Topiramate</td>
<td>No</td>
<td>-</td>
<td>Medication preference or intolerance/no response to naltrexone and acamprosate</td>
<td>Medication preference or intolerance/no response to naltrexone and acamprosate</td>
<td>Unknown, multiple targets</td>
<td>Initial: 50 mg daily Maintenance: Titrate to max of 100 mg BID</td>
<td>Alcohol use 6 hours before or after medication administration *Only with Trokendi XR</td>
<td>-LFT and EKG at baseline -Repeat LFT at 1 month, 6 months, annually</td>
<td>N/A</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>No</td>
<td>-</td>
<td>Medication preference or intolerance/no response to naltrexone and acamprosate</td>
<td>Medication preference or intolerance/no response to naltrexone and acamprosate</td>
<td>GABA analog</td>
<td>Initial: 300 mg daily Maintenance: Titrate by 300 mg every 1-2 days to target of 600 mg TID</td>
<td>None</td>
<td>-Behavioral changes indicative of suicidality or depression</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* Avoid antidepressants and benzodiazepines for AUD treatment unless comorbidity with therapeutic indication present (1B and 1C recommendations, respectively)
ii) Limitations of evidence-based pharmacotherapy

1) Naltrexone\textsuperscript{20-22}
   (a) Tolerability limited by nausea and headache
   (b) Study evaluating efficacy of long-acting injectable naltrexone found slight reduction of heavy drinking days in men, none in women

2) Acamprosate\textsuperscript{23-25}
   (a) Meta-analysis revealed wide variability in efficacy across studies, with slight increase in odds of abstinence vs. placebo when all data included
   (b) Large multisite trial excluded from meta-analysis failed to demonstrate therapeutic efficacy
   (c) High pill burden

3) Disulfiram\textsuperscript{21,26-28}
   (a) Modest efficacy in drinking frequency reduction, no improvement in abstinence rates
   (b) Use limited by significant hepatotoxicity risk, need for regular LFT monitoring, and contraindication in ischemic heart disease

4) High relapse rate\textsuperscript{3,29}
   (a) 20-30\% of patients abstinent or in long-term remission without formal treatment
   (b) 40-70\% of patients relapse within first 12 months after treatment

iii) Novel therapeutic targets

<table>
<thead>
<tr>
<th>Therapeutic target</th>
<th>Medication</th>
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<tbody>
<tr>
<td>Alpha-1 adrenergic receptors</td>
<td>Doxazosin, prazosin</td>
</tr>
<tr>
<td>Voltage-gated calcium channels</td>
<td>Gabapentin</td>
</tr>
<tr>
<td>GABA receptors</td>
<td>Baclofen, diazepam</td>
</tr>
<tr>
<td>Glutamate receptors</td>
<td>Glycine, ifenprodil, memantine</td>
</tr>
<tr>
<td>Neuroendocrine pathways</td>
<td>ABT-436 (novel vasopressin receptor 1b antagonist), oxytocin (intranasal), PF-5190457 (novel ghrelin receptor inverse agonist)</td>
</tr>
<tr>
<td>Nicotinic acetylcholine receptors</td>
<td>Mecamylamine, varenicline</td>
</tr>
<tr>
<td>Multiple targets</td>
<td>Aripiprazole, quetiapine, topiramate</td>
</tr>
<tr>
<td>Other medications</td>
<td>Citoline, ibudilast, N-acetylcysteine, samidorphan</td>
</tr>
</tbody>
</table>
II. Prazosin (Minipress®)

1) Indications (see Appendix 2 for dosing information)
   a) Adults
      i) Hypertension (not recommended as first-line agent per guidelines)
      ii) PTSD-related nightmares and sleep disruption (off-label use)
      iii) Raynaud phenomenon (off-label use)
   b) Pediatrics (limited data available)
      i) Hypertension unresponsive to trials of ≥ 2 guideline-preferred antihypertensive agents
      ii) Scorpion envenomation

2) Mechanism of action
   a) Competitive inhibition of postsynaptic alpha-1 adrenergic receptors in vascular smooth muscle
      i) Causes vasodilation of peripheral veins and arterioles
      ii) Leads to decreased total peripheral resistance and BP

3) Precautions
   a) Angina
   b) CNS depression
   c) Floppy iris syndrome: No benefit in therapy discontinuation prior to cataract surgery
   d) Heart failure: May exacerbate underlying myocardial dysfunction due to prolonged elimination
   e) Orthostatic hypotension/syncope: Per Beers Criteria, avoid use as anti-hypertensive in geriatrics
   f) Priapism
   g) Prostate cancer: Rule out prostate cancer prior to initiation

4) Adverse effects
   a) Dizziness (10.3%)
   b) Headache (7.8%)
   c) Drowsiness (7.6%)
   d) Decreased energy (6.9%)
   e) Weakness (6.5%)
   f) Palpitations (5.3%)
   g) Nausea (4.9%)

5) Monitoring parameters
   a) BP

6) Pharmacokinetics
   a) Absorption
      i) Onset of action: Within 2 hours
         (1) Peak effect: 2-4 hours
         (2) Duration of action: 10-24 hours
      ii) Bioavailability: 43-82%
   b) Distribution: \( V_d \) of 0.5 L/kg
      i) 97% protein bound
   c) Metabolism: Hepatic via demethylation and conjugation
   d) Excretion: Feces and urine (6-10% as unchanged drug)
      i) Half-life elimination: 2-3 hours

Figure 3. Chemical structure of prazosin
http://drugcentral.org/drug/4209/image
III. Clinical question

**Can prazosin be used as an alternative treatment for AUD?**

1) Proposed mechanism for targeting AUD
   a) AUD pathophysiology\(^3,31,32\)
      i) Mediated by mesolimbic reward pathway
         (1) Serotonin (5-HT) dysfunction due to disrupted neurotransmission
         (2) Down-regulation of inhibitory GABA receptors
         (3) Up-regulation of excitatory glutamate receptors
         (4) Other affected neurotransmitter systems: \(\gamma\)-aminobutyric acid, endogenous opioids, cannabinoids, norepinephrine
   b) Abrupt alcohol cessation causes brain hyperexcitability due to increased secretion of cortisol and corticotropin releasing factor\(^3,33\)
      i) Experimental and clinical results established hyperexcitability as key feature in AUD predisposition
      ii) Hyperexcitability associated with increased adrenergic activation
   c) Initiation and maintenance of AUD associated with elevated noradrenergic activity in the brain\(^34-38\)
      (1) Preclinical evidence suggested noradrenergic systems have intimate involvement in various brain processes relevant to AUD\(^39-41\)
         (a) Arousal
         (b) Reinforcement
         (c) Stress responsivity
      (2) Noradrenergic systems modulate midbrain dopaminergic neurons which have key roles in reinforcing and locomotor activating responses to drugs of abuse, including alcohol\(^42\)
      (3) Research with recently abstinent alcohol dependent individuals found elevated plasma epinephrine and norepinephrine levels\(^43-45\)
   d) Prazosin decreases noradrenergic activity via reducing norepinephrine activation at post-
      synaptic alpha-1 adrenoreceptors\(^46-48\)
      i) Most lipid-soluble alpha-1 antagonist
      ii) Crosses blood brain barrier to decrease brain alpha-1 adrenoreceptor-mediated signaling
      iii) Demonstrated activity at CNS sites when administered peripherally

2) Development of prazosin as novel therapeutic agent
   a) Based on clinical observation of patients with co-occurring PTSD and AUD reporting substantially reduced and even complete cessation of alcohol consumption during prazosin treatment\(^42\)
   b) Hypothesis of prazosin utility in reducing both alcohol-induced reward and stress induced relapse tested in 2 animal models\(^35,49\)
      i) First preclinical study revealed decreased withdrawal-induced alcohol intake by Wistar rats with prazosin treatment
      ii) Second preclinical study demonstrated alcohol intake by alcohol-preerring rats with acute and chronic prazosin treatment
   c) Literature supporting prazosin as effective treatment alternative in humans is more recent\(^37,50\)
      i) In a human laboratory study, prazosin reduced craving, anxiety, and negative emotion induced by an alcohol cue and/or stressor relative to placebo
      ii) Decrease in percent DDPW and percent heavy DDPW vs. placebo in concurrent AUD and PTSD
   d) Literature involving other alpha-1 antagonists\(^38,51\)
      i) Doxazosin not effective in reducing drinking overall vs. placebo, but did reduce DPW and heavy drinking days in patients with positive family history of alcoholism
      ii) Doxazosin decreased DPDD in patients with elevated DBP

<table>
<thead>
<tr>
<th>Objective</th>
<th>Determine whether prazosin is an effective pharmacological agent for reducing drinking in AD and its impact on craving</th>
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<tbody>
<tr>
<td>Hypothesis</td>
<td>Prazosin is an effective AD treatment and should at least modulate or reduce cravings due to antagonizing central postsynaptic $\alpha_1$ activity</td>
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### Methods

#### Study design

6-week double-blind, randomized pilot study

#### Patient population

**Inclusion criteria:**
- 18-69 years old
- Confirmed current DSM-IV AD
- Last alcohol use within 1 month
- Treatment seeking for AD
- Females of childbearing age if reported effective contraception use

**Exclusion criteria:**
- Confirmed PTSD diagnosis
- Psychiatric disorder requiring medication initiation at time of study entry other than antidepressants
- Current diagnosis of opioid dependence or abuse
- SBP < 110 mmHg or preexisting orthostatic BP
- Unstable angina, Meniere’s disease, narcolepsy, benign positional vertigo, chronic renal or hepatic failure, pancreatitis or insulin-dependent diabetes, or other medical problems requiring immediate attention
- Any concurrent AD treatment, except Alcoholics Anonymous

#### Intervention

- Recruitment from 11/2005-08/2007 via newspaper advertisements, flyers at VA Puget Sound Healthcare System, and announcements during Addiction Treatment Center orientation group meetings
- Participant screening after passing breathalyzer test to rule out intoxication
  - Physical exam (weight, height, vital signs)
  - Psychiatric and medical history
  - DSM-IV PTSD checklist for substance dependence and abuse, PTSD section of structured clinical interview for DSM-IV if positive PTSD screen
- Baseline assessment of eligible participants (same day or within following week)
  - Demographic information interview
  - 6-week Form-90 (Form-42) for use of alcohol and illicit drugs
  - PACS and PACS modified for cocaine and marijuana
  - Labs: Complete blood count, electrolytes, LFT, urine pregnancy, and urine toxicology
- Participant randomization to placebo or prazosin groups by facility research pharmacist
  - Prazosin titrated to target dose of 4 mg QAM, 4 mg QPM, and 8 mg QHS (or highest tolerated dose) by end of week 2 then continued on stable dose for additional 4 weeks
- Daily IVR telephone monitoring to report alcohol, marijuana, and cocaine use/craving, medication compliance, and general emotional well-being
- Study visits twice weekly during initial 2 weeks and weekly thereafter
  - Urine collection and assessment of compliance, orthostatics, and adverse events at each visit
  - Repeat LFT at end of weeks 3 and 6
  - Repeat PACS and Form-42 at end of week 6
  - Participant inquiry regarding thoughts about treatment group assignment at end of week 6 and level of certainty via visual analog scale
- 5 counseling visits using Medical Management protocol
  - Initial 30-45 minute session and 10-minute follow-up sessions at weeks 1, 2, 4, and 6

#### Outcomes

Self-reported alcohol consumption and cravings

#### Statistical analysis

- Demographic, baseline, and compliance variables analyzed with descriptive statistics
- Differences between treatment groups analyzed with chi-square test for categorical variables and student’s t-test for continuous variables
  - Adverse events, BP changes, craving changes between baseline and week 6 (as measured by PACS)
- Multilevel mixed-effects linear regression models analyzed changes over study course, analyses adjusted for DDPW and DPW at baseline and week number
  - Changes over study course in DDPW and DPW reported via daily IVR
  - Changes over last 3 weeks in DDPW and DPW
  - Changes over study course in craving and craving resistance as measured by daily IVR
- Statistical significance defined as two-sided p-values < 0.05

### Results

**Baseline characteristics**

- n = 24 (19 males, 5 females)
  - Mean age = 45.5 ± 8 years
  - Mild AD = 12.5%, moderate AD = 54.2%, severe AD = 33.3%
  - 83% Caucasian, 87.5% living at home, 25% married, 33.3% veterans
  - No significant differences in demographics, average number of drinking days, average number of heavy days drinking, average SDU reported, or AD severity per number of DSM-IV criteria present
- 83.3% participants completed trial (n = 20)
  - Prazosin group = 9 (7 males, 2 females), placebo group = 11 (10 males, 1 female)
  - 1 participant (assigned placebo) withdrew after 3 days
  - 2 participants (assigned prazosin) withdrew after 3 weeks due to inability to attend required visits
  - 1 participant (assigned prazosin) discharged from study due to compromising study protocol
  - Only 1 participant did not reach target dose
  - Medication compliance: Prazosin group = 92%, placebo group = 87%
  - No significant differences between groups in number of Medical Management visits completed or number of vital signs/lab visits attended

**Outcomes**

- Among all study completers (n = 20)
  - Alcohol use decreased by ~2.78 mean DPW (95% CI = -4.01 to -0.55; p = 0.010) and 0.40 DDPW (95% CI = -0.61 to -0.19; p < 0.001)
  - DDPW: Fewer in prazosin vs. placebo group during final 3 weeks (β = -1.22; 95% CI = -2.29 to -0.14; p = 0.027)
    - Average total number drinking days of 3.2 (SEM 1.9) in prazosin vs. 5.6 (SEM 1.9) in placebo group
  - DPW: No differences between groups during final 3 weeks
  - Mean craving decreased by ~0.93 points (95% CI = -1.55 to -0.31; p = 0.003) over 6 weeks; craving did not differ by condition
  - No changes in mean craving resistance per week after adjusting for mean craving; craving resistance did not differ between conditions
- Final analysis included male completers, females excluded (n = 17)
  - 6 of 7 males in prazosin group abstinent at week 6 (1 abstinent during entire study period)
  - 4 of 10 males in placebo group abstinent at week 6 (3 abstinent during entire study period)
  - DDPW: Fewer in prazosin vs. placebo group during final 3 weeks (β = -1.84; 95% CI = -2.74 to -0.93; p < 0.001)
    - Average total number drinking days of 0.9 (SEM 0.5) in prazosin vs. 5.7 (SEM 1.9) in placebo group
  - DPW: Fewer in prazosin vs. placebo group during final 3 weeks after adjusting for DPW at baseline and week number (β = -4.59; 95% CI = -8.86 to -0.31; p = 0.035)
    - Average total number drinks of 2.6 (SEM 1.3) in prazosin vs. 20.8 (SEM 6.5) in placebo group
  - Mean craving decreased by ~0.90 points (95% CI = -1.48 to -0.31; p = 0.003) over 6 weeks; craving did not differ by condition
  - No changes in mean craving resistance per week after adjusting for mean craving, however greater increases over time in mean craving resistance per week in prazosin group after adjusting for mean craving per week (β = 0.36; 95% CI = 0.01-0.70; p = 0.043)
- Equivalent adverse event rates across conditions (most frequent: dizziness, lack of energy, drowsiness)
Discussion

Critique

Strengths:
- Randomized, double-blind study design
- Exclusion of PTSD comorbidity and concurrent AD treatment
- Ability to control type and amount of behavioral treatment through medical management sessions
- Use of IVR as daily monitoring data collection system
- Frequent follow-up and successful titration to target dose in nearly all participants
- Appropriate adjustment of analyses

Limitations:
- Small sample size and uneven gender distribution
- Randomization did not consider patient characteristics
- Medication intervention period limited to 6 weeks
- Lack of long-term follow-up limits insight into persistence of medication effects and relapse risk
- Inclusion of 4 abstinent participants (prazosin = 1, placebo = 3) limits evaluation of medication efficacy on drinking outcomes
- Limited generalizability due to overall sample with “levels of consumption on the lower end of the spectrum for AD”
- Limited extrapolation to females due to omission in final analysis as well as non-Caucasians
- Results heavily dependent on participant self-reports
- Collection of LFT instead of more sensitive GGT levels
- Baseline characteristics not fully reported
- DSM-IV obsolete, AUD criteria differ per current DSM-V

Conclusions

Authors:
- Prazosin holds promise as a pharmacologic treatment for AD and deserves further evaluation in a larger controlled trial

Reviewer:
- Positive findings for prazosin among AD patients without PTSD and use of other concurrent medication treatment suggests medication efficacy and validates novel therapeutic target
- Study results do not allow for definitive conclusions due to short medication intervention period and lack of long-term follow-up of pilot study as well as inability to extrapolate results to certain populations
- Additional studies with larger sample size and longer follow-up warranted to better evaluate medication efficacy and safety


| Objective | Determine whether prazosin can treat AUD in a larger sample size based on prior positive pilot study |
| Hypothesis | Over time, prazosin leads to decreased likelihood of any drinking and heavy drinking (≥ 5 drinks for males, ≥ 4 drinks for females) as well as decrease in number of drinks consumed |

**Methods**

| Study design | 12-week outpatient, double-blind, randomized controlled trial |

**Patient population**

**Inclusion criteria:**
- Current DSM-IV diagnosis of alcohol dependence
- Alcohol consumption during 4 consecutive weeks within 90 days
  - Males ≥ 21 DPW
  - Females ≥ 14 DPW
  - 2 occasions of heavy drinking
- Goal of alcohol abstinence
- Females of childbearing age if reported effective contraception use

**Exclusion criteria:**
- Current DSM-IV diagnosis of PTSD
- Uncontrolled psychiatric disorder with psychotic symptoms or cognitive impairment
- Unstable psychiatric medication dosing within 1 month
- Use of alcohol abstinence medications (disulfiram, acamprosate, naltrexone) within 1 month
- Current opioid dependence, use of opioids within 1 month, or positive urine screen for opioids, benzodiazepines, or sedative-hypnotics
- Significant acute or chronic illness
- SBP < 100 mmHg or orthostatic hypotension
- Prazosin sensitivity or use of prazosin within 30 days
- Use of trazodone, tadalafil, or vardenafil in males
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Participation in drug or addiction study within 1 month</th>
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<tbody>
<tr>
<td></td>
<td>Any concurrent behavioral or medication AUD treatment,</td>
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<tr>
<td></td>
<td>except Alcoholics Anonymous and supportive counseling</td>
</tr>
<tr>
<td>Recruitment from 01/2008-05/2014 via clinical referrals, flyers, and newspaper/Craigslist advertisements</td>
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<tr>
<td>Participant eligibility determined via telephone screening</td>
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<tr>
<td>Baseline assessment of eligible participants within 1 week</td>
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<tr>
<td>Participant randomization (stratified by gender, veteran status, and drinking frequency [&lt; 10 days or ≥ 10 days within 30 days]) to placebo or prazosin groups by facility research pharmacist</td>
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</tr>
<tr>
<td>o Prazosin titrated to target dose of 4 mg QAM, 4 mg QPM, and 8 mg QHS (or highest tolerated dose) by end of week 2 then continued on stable dose for additional 10 weeks</td>
<td></td>
</tr>
<tr>
<td>Daily IVR telephone monitoring to report alcohol consumption, cravings, and medication compliance</td>
<td></td>
</tr>
<tr>
<td>Study visits twice weekly during initial 2 weeks and weekly thereafter</td>
<td></td>
</tr>
<tr>
<td>o Urine collection and assessment of compliance, orthostatics, and adverse events at each visit</td>
<td></td>
</tr>
<tr>
<td>Weekly medical management counseling emphasizing adherence and self-help meeting attendance</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>Primary (aggregated to weekly level)</td>
</tr>
<tr>
<td></td>
<td>o Number DPW</td>
</tr>
<tr>
<td></td>
<td>o Number DDPW</td>
</tr>
<tr>
<td></td>
<td>o Number heavy DDPW</td>
</tr>
<tr>
<td>Secondary (aggregated to weekly level)</td>
<td></td>
</tr>
<tr>
<td>o Mean of 4 daily craving items (thinking about drinking, strength of craving, difficulty resisting drinking, self-reported average craving), each rated on 0-8 scale</td>
<td></td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>Demographic and baseline information analyzed with descriptive statistics, including percentages for categorical variables and means/standard deviations for continuous variables</td>
</tr>
<tr>
<td></td>
<td>Differences between treatment groups analyzed with chi-square test for categorical variables and student’s t-test for continuous variables</td>
</tr>
<tr>
<td></td>
<td>Generalized linear mixed-effects models examined primary and secondary outcome changes between treatment groups over study course, model results summarized by adjusted marginal means</td>
</tr>
<tr>
<td></td>
<td>4 sensitivity analyses performed for primary outcomes</td>
</tr>
<tr>
<td></td>
<td>Exploratory analyses performed to analyze change in standing BP using linear mixed-effects models</td>
</tr>
<tr>
<td>Results</td>
<td>n = 92 (73 males, 19 females)</td>
</tr>
<tr>
<td></td>
<td>o Prazosin group = 48 (mean age = 47.3 ± 9.8 years), placebo group = 44 (mean age = 49.1 ± 9.5 years)</td>
</tr>
<tr>
<td></td>
<td>o No significant differences in demographic or baseline drinking variables (p &gt; 0.26 for all)</td>
</tr>
<tr>
<td></td>
<td>80 completed 2-week titration period and included in primary analyses</td>
</tr>
<tr>
<td></td>
<td>o Prazosin group = 40, placebo group = 40</td>
</tr>
<tr>
<td></td>
<td>12 participants withdrew during titration period</td>
</tr>
<tr>
<td></td>
<td>o 70 participants reached target dose (prazosin group = 35, placebo group = 35)</td>
</tr>
<tr>
<td></td>
<td>o 56 participants completed 12-week study period (prazosin group = 26, placebo group = 30)</td>
</tr>
<tr>
<td></td>
<td>▪ Mean participation duration of 10.4 ± 2.7 weeks for prazosin vs. 10.5 ± 3 weeks for prazosin group</td>
</tr>
<tr>
<td></td>
<td>o Medication compliance to TID dosing: Prazosin = 54.7% of days, placebo = 69.7% of days (p = 0.04)</td>
</tr>
</tbody>
</table>
### Outcomes

- **Primary**
  - No difference in craving change over time between groups

- **Secondary**
  - No difference in craving change over time between groups
  - Sensitivity analyses
    - Results similar to primary analyses, but no condition-by-week interactions significant for random-slopes models ($p \geq 0.25$ for all)
  - Exploratory analyses
    - SBP decrease by mean of 3.5 mmHg in prazosin group, increase by mean of 3.1 mmHg in placebo group
      - 6.6 mmHg difference between conditions (condition-by-week interaction, $X^2 = 6.1$, $df = 1$, $p = 0.01$)
    - No significant change in DBP between groups ($p > 0.11$)
    - No significant difference in change by condition ($p > 0.26$)
    - Neither SBP nor DBP was significant effect modifier in difference in improvement in total number of drinks or heavy drinking days by condition (3-way blood pressure-by-condition-by-week interactions, $p$ values $> 0.26$ for all)
  - 5 serious adverse events, none deemed to be related to study involvement though 2 participants assigned to prazosin group hospitalized for alcohol withdrawal
  - Significantly more drowsiness ($p = 0.020$) and edema ($p = 0.036$) in prazosin vs. placebo group

### Table 2. Adjusted Marginal Means and Differences in Weekly Drinking Outcomes After Titration and at End of Study in a Placebo-Controlled Trial of Prazosin for Alcohol Use Disorder

<table>
<thead>
<tr>
<th>Drinking Outcome</th>
<th>Prazosin Group (N=40)</th>
<th>Placebo Group (N=40)</th>
<th>Difference in Change $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 3 Mean</td>
<td>Week 12 Mean</td>
<td>Mean</td>
</tr>
<tr>
<td>Number of drinks per week</td>
<td>21.3</td>
<td>13.3</td>
<td>8.0</td>
</tr>
<tr>
<td>Number of drinking days per week</td>
<td>3.2</td>
<td>2.8</td>
<td>0.4</td>
</tr>
<tr>
<td>Number of heavy drinking days per week</td>
<td>1.8</td>
<td>1.0</td>
<td>0.8</td>
</tr>
</tbody>
</table>

### Discussion

#### Critique

- **Strengths:**
  - Randomized, double-blind study design
  - Similar interventions compared to pilot study facilitated comparison of results
  - Exclusion of PTSD comorbidity and concurrent AUD treatment
  - Larger sample size and longer study period compared to pilot study
  - Randomization took into account patient characteristics

- **Limitations:**
  - Lacking knowledge about optimal prazosin dosing in AUD
  - Short titration period without placebo washout period, lack of long-term follow-up limits insight into persistence of medication effects and relapse risk
  - Poor medication adherence
  - Participants varied widely in both AUD severity and recent drinking patterns
  - Random-slope models showed no differences between treatment groups, unlike fixed-slope models
  - Results heavily dependent on participant self-reports
  - DSM-IV obsolete, AUD criteria differ per current DSM-V

#### Authors:

- Greater decrease over time in rate of drinking and probability of heavy drinking with prazosin vs. placebo, but not in number of drinking days per week

#### Reviewer:

- Larger and longer study supports use of prazosin as harm-reduction pharmacologic treatment for AUD and deserves further evaluation by independent research groups

| Objectives | • Measure effects of prazosin on drinking and provide further information on safety and tolerability in AUD  
• Examine several potential treatment moderators for prazosin |
| Hypothesis | High baseline DBP and anxiety predict more robust treatment response |
| Methods | 45-day randomized, double-blind, placebo-controlled trial at University of New Mexico Center for Psychiatric Research |

### Patient population

**Inclusion criteria:**
- 18-65 years old  
- English-speaking  
- Treatment seeking (cut back or quit alcohol)  
- ≥ 4 heavy drinking days (> 5 standard drinks for men, > 4 standard drinks for women) within 1 month  
- Meet criteria for AD within 3 months

**Exclusion criteria:**
- Concurrent alcohol treatment  
- Concurrent antidepressant, anti-craving, anxiolytic, antipsychotic, mood-stabilizing, or anticonvulsant use  
- Severe neurologic, cardiac, hepatic, or renal medical issues or other serious medical conditions  
- Comorbid diagnoses of PTSD, schizophrenia, schizoaffective disorder, bipolar I, or dependence on another drug other than nicotine or cannabis  
- Suicidal thoughts within 1 month  
- Pregnant

### Intervention

- Recruitment from 09/2013-05/2016 via newspapers, flyers, and online postings/Craigslist  
- Participant eligibility determined via telephone pre-screening and in-person screening  
- Participant randomization (stratified by presence of anxiety disorder diagnosis) to placebo or prazosin groups by facility research pharmacist  
  - Prazosin titrated to target dose of 16 mg daily (or highest tolerated dose) by end of week 2 then continued on stable dose for additional 4 weeks  
- 8 Medical Management visits (6 in-person, 2 via phone)  
  - Participant inquiry regarding thoughts about treatment group assignment at end of week 6  
- Full and adjusted medication adherence measured via pill counts and self-report

### Outcomes

- Primary  
  - DPW  
- Secondary  
  - DPDD  
  - PDA  
  - PHDD

### Statistical analysis

- Hierarchical linear modelling used to examine effect of treatment group on rate of change in primary and several secondary outcome measures  
- Statistical significance defined as p-values < 0.05  
- Exploratory post-hoc analyses in subgroup with adequate medication exposure and smaller subgroup after outlier exclusion

### Results

- 36 participants initiated medications  
  - Prazosin group = 18 (mean age = 38.6 ± 12.4 years), placebo group = 18 (mean age = 40.7 ± 10.7 years)  
  - No significant differences in baseline characteristics or tested variables  
- 33 participants confirmed as starting medication therapy (prazosin group = 17, placebo group = 16)  
  - 1 participant dropped, 2 others lost to follow-up  
- 27 participants completed 6-week study period (prazosin group = 13, placebo group = 14)  
  - 6 participants lost to follow-up, 4 others discontinued prazosin due to side effects/adverse events but completed study
**Outcomes**

- **Primary**
  - No significant difference in alcohol use rate of reduction in intent-to-treat sample vs. placebo (n = 36)
  - Prazosin significantly increased rate of reduction in DPW in optimal treatment exposure subgroup (n = 27; \( \beta = -0.3, P = 0.01 \), event rate ratio 0.74, CI 0.59-0.93) after post-hoc analysis

- **Secondary**
  - No significant difference in alcohol use rate of reduction in intent-to-treat sample or optimal treatment exposure subgroup vs. placebo

- **Moderator analyses**
  - Sitting DBP (p = 0.038) and standing DBP (p = 0.024) significantly moderated effect of medication condition on rate of change in DPDD
    - Prazosin associated with significantly greater rates of reduction in drinking vs. placebo in individuals with high DBP (standing or sitting)

**Discussion**

**Strengths:**
- Randomized, double-blind study design
- Exclusion of PTSD comorbidity with inclusion of other concurrent SUD improves generalizability
- Similar interventions compared to pilot study facilitated comparison of results
- Randomization took into account patient characteristics

**Limitations:**
- Poor adherence and tolerability
- Small sample size with insufficient power to detect small effects
- Medication intervention period limited to 6 weeks
- Lack of long-term follow-up limits insight into persistence of medication effects and relapse risk
- Response heterogeneity in moderator analyses may have masked or contributed to false positive results
- Bias in direction of finding treatment effect
- DSM-IV obsolete, AUD criteria differ per current DSM-V; no distinction of AD severity at baseline

**Critique**

**Authors:**
- Prazosin might have some efficacy in individuals with high DBP

**Reviewer:**
- Study results do not allow for definitive conclusions due to small sample size, short medication intervention period, and poor adherence rates
- Additional studies with larger sample size and longer follow-up warranted to better evaluate medication efficacy and safety

**Conclusions**

**Reviewers:**
- Prazosin might have some efficacy in individuals with high DBP

**Reviewer:**
- Study results do not allow for definitive conclusions due to small sample size, short medication intervention period, and poor adherence rates
- Additional studies with larger sample size and longer follow-up warranted to better evaluate medication efficacy and safety

**Table 9. Summary of study outcomes**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intent-to-treat group</td>
<td>Optimal treatment subgroup</td>
<td></td>
</tr>
<tr>
<td>DDPW</td>
<td>↓*</td>
<td>-*</td>
<td>N/A</td>
</tr>
<tr>
<td>DPW</td>
<td>↓*</td>
<td>↓*</td>
<td>-*</td>
</tr>
<tr>
<td>Heavy DDPW</td>
<td>N/A</td>
<td>↓*</td>
<td>N/A</td>
</tr>
<tr>
<td>Craving</td>
<td>↓*</td>
<td>-**</td>
<td>N/A</td>
</tr>
<tr>
<td>DPDD</td>
<td>N/A</td>
<td>N/A</td>
<td>-**</td>
</tr>
<tr>
<td>PDA</td>
<td>N/A</td>
<td>N/A</td>
<td>-**</td>
</tr>
<tr>
<td>PHDD</td>
<td>N/A</td>
<td>N/A</td>
<td>-**</td>
</tr>
<tr>
<td>Adverse events</td>
<td>—</td>
<td>↑ (drowsiness, edema)</td>
<td>N/A</td>
</tr>
<tr>
<td>BP changes</td>
<td>N/A</td>
<td>—</td>
<td>↓ (DBP)</td>
</tr>
</tbody>
</table>

* Primary outcome
** Secondary outcome
**IV. Conclusion**

1) Prazosin shows promise as effective treatment alternative for AUD
   a) Facilitates increase in rate of reduction in drinks per week and an overall decrease in drinking rate over time, facilitating harm reduction
   b) Studies support efficacy independent of concurrent PTSD diagnosis, but limitations exist
      i) Lack of robust literature
      ii) Small sample sizes
      iii) Short-term medication intervention
      iv) Lack of rationale for high starting and/or target dose without more gradual up-titration
      v) Lack of long-term follow-up
      vi) Adherence issues
      vii) Use of outdated DSM-IV criteria
      viii) Lack of insight into treatment efficacy based on AUD severity
      ix) No available literature evaluating efficacy of prazosin monotherapy vs. adjunctive use

**V. Recommendation**

1) Despite study limitations, prazosin appears to be worthwhile third-line agent to consider for AUD with less limitations to use compared to current first- and second-line agents
   a) Treatment goal: Reduction in alcohol consumption
   b) Place in therapy: Medication preference or intolerance/no response to current evidence-based first- and second-line agents

<table>
<thead>
<tr>
<th>Table 10. Treatment considerations for prazosin in AUD treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Consider use</strong></td>
</tr>
<tr>
<td>• Confirmed AUD per DSM criteria</td>
</tr>
<tr>
<td>• Treatment failure or contraindications to current approved and/or evidence-based treatment alternatives</td>
</tr>
<tr>
<td>• +/- non-pharmacological interventions</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

   c) Dosing
      i) Target dose of 4 mg QAM, 4 mg QPM, and 8 mg QHS
      ii) Highest tolerated dose if concerns/issues arise during treatment

d) Duration
   i) At least 6-12 weeks based on current literature
   ii) May consider stopping medication at course completion and restarting with indefinite treatment if relapse occurs

e) Monitoring parameters
   i) BP and orthostatics
   ii) Drowsiness
   iii) Edema
   iv) LFT and GGT at baseline and 6 weeks
VI. Future direction

1) Evaluate AUD severity and baseline BP as moderators of treatment response in larger sample size
2) Establish optimal dosing regimens and whether target dose of 16mg daily is necessary, taking into account AUD severity at baseline
3) Establish optimal duration of treatment and risk of relapse through long-term follow-up
4) Pending clinical trials

Table 11. Prazosin augmentation of outpatient treatment of alcohol use disorders in active duty soldiers with and without PTSD

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>NCT02226367</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td></td>
<td>Started January 2015</td>
</tr>
<tr>
<td></td>
<td>Estimated completion December 2019</td>
</tr>
<tr>
<td>Objective</td>
<td>Evaluate efficacy of prazosin for decreasing alcohol use in active duty military members who served in Iraq and/or Afghanistan and determine if presence or absence of PTSD affects treatment</td>
</tr>
<tr>
<td>Hypotheses</td>
<td>Prazosin is more effective than placebo for AUD in military service members</td>
</tr>
<tr>
<td></td>
<td>Prazosin effect size is greater in military service members with PTSD than without PTSD</td>
</tr>
<tr>
<td>Study design</td>
<td>19-week, titration to stable dose, randomized, 2-group parallel-design, double-blind, placebo-controlled trial</td>
</tr>
<tr>
<td>Intervention</td>
<td>Prazosin titrated to maximum dose of 4 mg QAM, 6 mg QPM, and 10 mg QHS vs. placebo</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Change in PACS score at week 13 from baseline</td>
</tr>
</tbody>
</table>

Table 12. Effect of prazosin and naltrexone on personalized script-induced alcohol craving in individuals with alcohol use disorders with and without comorbid PTSD

<table>
<thead>
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<th>Trial ID</th>
<th>NCT02322047</th>
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<tbody>
<tr>
<td>Status</td>
<td>Recruiting</td>
</tr>
<tr>
<td></td>
<td>Started November 2014</td>
</tr>
<tr>
<td>Objective</td>
<td>Evaluate whether prazosin and naltrexone will decrease alcohol cravings and drinking in individuals who have problems with alcohol and have used alcohol at risky levels in the past 90 days</td>
</tr>
<tr>
<td>Study design</td>
<td>Double-blind, double-dummy, placebo controlled phase 2 study</td>
</tr>
<tr>
<td>Intervention</td>
<td>Experimental arm: Prazosin and naltrexone</td>
</tr>
<tr>
<td></td>
<td>o Prazosin dosing</td>
</tr>
<tr>
<td></td>
<td>▪ Days 1-2: 1 mg @ 9PM</td>
</tr>
<tr>
<td></td>
<td>▪ Days 3-4: 1 mg @ 9AM, 3PM, 9PM</td>
</tr>
<tr>
<td></td>
<td>▪ Days 5-7: 2 mg @ 9AM, 3PM, 9PM</td>
</tr>
<tr>
<td></td>
<td>o Naltrexone dosing</td>
</tr>
<tr>
<td></td>
<td>▪ Days 1-49: 50mg @ 9PM</td>
</tr>
<tr>
<td></td>
<td>Active comparator arms</td>
</tr>
<tr>
<td></td>
<td>o Prazosin and placebo (naltrexone)</td>
</tr>
<tr>
<td></td>
<td>o Naltrexone and placebo (prazosin)</td>
</tr>
<tr>
<td></td>
<td>Placebo arm: Placebo (prazosin) and placebo (naltrexone)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Alcohol consumption in standard drinks (daily assessment over 7 weeks)</td>
</tr>
<tr>
<td></td>
<td>Alcohol craving using Likert scale of 0-8 (daily assessment over 7 weeks)</td>
</tr>
</tbody>
</table>
References


Appendix 1. List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD</td>
<td>Alcohol dependence</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>APA</td>
<td>American Psychiatric Association</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>AUD</td>
<td>Alcohol use disorder</td>
</tr>
<tr>
<td>AUDIT</td>
<td>Alcohol use disorders identification test</td>
</tr>
<tr>
<td>AUDIT-C</td>
<td>Alcohol use disorders identification test-consumption</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
</tr>
<tr>
<td>DDPW</td>
<td>Drinking days per week</td>
</tr>
<tr>
<td>DPDD</td>
<td>Drinks per drinking day</td>
</tr>
<tr>
<td>DPW</td>
<td>Drinks per week</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>EKG</td>
<td>Electrocardiography</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GABA</td>
<td>Gamma-aminobutyric acid</td>
</tr>
<tr>
<td>GGT</td>
<td>Gamma glutamyl transferase</td>
</tr>
<tr>
<td>INR</td>
<td>International normalized ratio</td>
</tr>
<tr>
<td>IVR</td>
<td>Interactive voice response</td>
</tr>
<tr>
<td>LFT</td>
<td>Liver function tests</td>
</tr>
<tr>
<td>PACS</td>
<td>Pennsylvania alcohol craving scale</td>
</tr>
<tr>
<td>PDA</td>
<td>Percent days abstinent</td>
</tr>
<tr>
<td>PHDD</td>
<td>Percent heavy drinking days</td>
</tr>
<tr>
<td>PTSD</td>
<td>Posttraumatic stress disorder</td>
</tr>
<tr>
<td>REMS</td>
<td>Risk evaluation and mitigation strategy</td>
</tr>
<tr>
<td>SASQ</td>
<td>Single alcohol screening questionnaire</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>SCr</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>SDU</td>
<td>Standard drink unit</td>
</tr>
<tr>
<td>SUD</td>
<td>Substance use disorder</td>
</tr>
<tr>
<td>US</td>
<td>United States</td>
</tr>
</tbody>
</table>

Appendix 2. Prazosin dosing based on indication

<table>
<thead>
<tr>
<th>Indication</th>
<th>Initial dose</th>
<th>Usual dose range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Adult: 1 mg PO BID-TID</td>
<td>Adult: Titrate up to 20 mg daily in 2-3 divided doses based on response and tolerability; may titrate up to 40 mg daily in some patients *With concomitant use of other antihypertensive agents or diuretics, decrease to 1-2 mg TID and re-titrare</td>
</tr>
<tr>
<td>Pediatric: 0.05-0.1 mg/kg/day PO in 3 divided doses</td>
<td>Pediatric: May titrate up to 0.5 mg/kg/day in 3 divided doses (max: 20 mg/day)</td>
<td></td>
</tr>
<tr>
<td>PTSD-related nightmares and sleep disruption (off-label use)</td>
<td>1 mg PO QHS, titrate to 2 mg QHS after 2-3 days, then titrate by 1-5 mg weekly based on response and tolerability</td>
<td>3-15 mg QHS (max: 15 mg/day)</td>
</tr>
<tr>
<td>Raynaud phenomenon (off-label use)</td>
<td>0.5-1 mg PO QHS or 0.5 mg PO BID</td>
<td>Titrate up to 12 mg/day in 2-3 divided doses based on response and tolerability</td>
</tr>
<tr>
<td>Scorpion envenomation</td>
<td>Weight-directed (infants ≥ 4 months, children, adolescents): 0.03 mg/kg/dose PO; second dose administered 3 or 6 hours after initial with subsequent doses Q3-6H for total of 48 hours or until extremities warm and dry Fixed dosing (infants &gt; 6 months, children, and adolescents): 0.25 mg PO Q3H until extremities warm and dry</td>
<td>N/A</td>
</tr>
</tbody>
</table>