Men vs Women:
Mental Health Considerations Among the Sexes

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9:30-11:00am G/T/C

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Outline & Objectives

1) Be able to describe and discuss the different prevalences of mental health issues among the sexes.

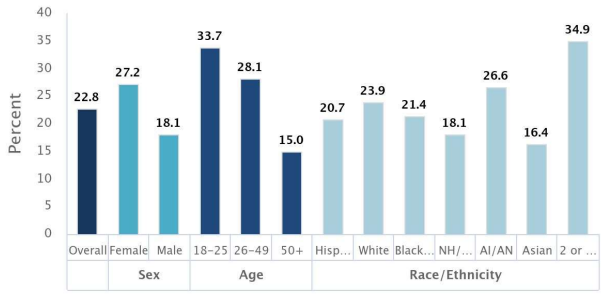
2) Recognize the factors influencing the different sexes with regards to their risk and presentation of mental illness.

3) Know the differences in psychotropic drug metabolism, possible dosing considerations between men and women, and specific treatments for disorders such as postpartum depression.

2

Past Year Prevalence of Any Mental Illness Among U.S. Adults (2021)

Data Courtesy of SAMHSA

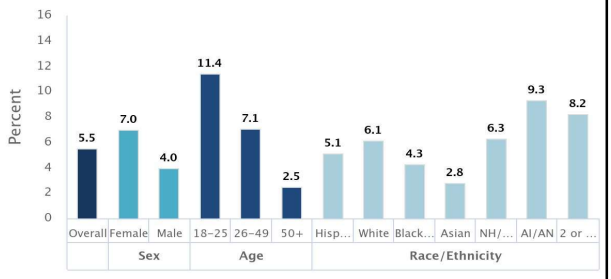


Mental Illness - National Institute of Mental Health (NIMH) (nih.gov)

3

Past Year Prevalence of Serious Mental Illness Among U.S. Adults (2021)

Data Courtesy of SAMHSA



Serious Mental Illness (SMI) – SMI is a smaller and more severe subset of mental illnesses; SMI is defined as one or more mental, behavioral, or emotional disorder(s) resulting in serious functional impairment, which substantially interferes with or limits one or more major life activities (NIMH)

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Severe Mental Illness (SMI)

- 1 in 5 Americans will experience a mental illness in a given year (CDC).
- Serious Mental Illness (SMI) – defined as one or more mental, behavioral, or emotional disorder(s) resulting in serious functional impairment, which substantially interferes with or limits one or more major life activities (NIMH).
- SMI includes major depression, schizophrenia, bipolar disorder, obsessive compulsive disorder (OCD), panic disorder, post traumatic stress (PTSD) and borderline personality disorder.
- ***These impairments often lead to an inability to maintain gainful employment, poor social support, repeated psychiatric hospitalizations, homelessness, incarceration, and coexisting substance use disorders.***

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Severe Mental Illness (SMI)

- 1 in 4 individuals with a SMI also have a substance use disorder (drugabuse.gov).
  - People with SMI are 4 times more likely to be heavy alcohol users (≥4 drinks per day);
  - 3.5 times more likely to use marijuana regularly (21 times per year);
  - 4.6 times more likely to use other drugs at least 10 times in their lives; and
  - 5.1 times more likely to be daily smokers (drugabuse.gov).
- Studies have shown that individuals with SMI show higher rates of acute and chronic illnesses, receive lower-quality general medical care, demonstrate worse long-term outcomes, and have a shorter life expectancy than the general population (VA).
- ***More than 75% of individuals with SMI have more than one mental illness, or a mental illness and a substance use or misuse condition*** (Kessler, Chiu, Demler, & Walters, 2005)

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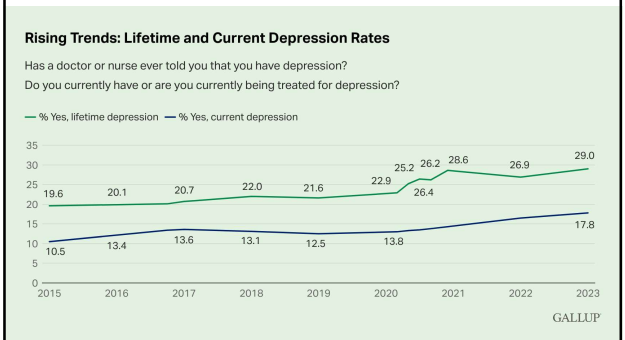
The Numbers: Lifetime Prevalence

Disorder	Men	Women
Depression	?	?
Generalized Anxiety	?	?
Bipolar Disorder	?	?
Schizophrenia	?	?
ADD/ADHD	?	?
PTSD	?	?
Substance Use Disorders		
Alcohol dependence (abuse)	?	?
Opioids	?	?
Benzodiazepines	?	?

8



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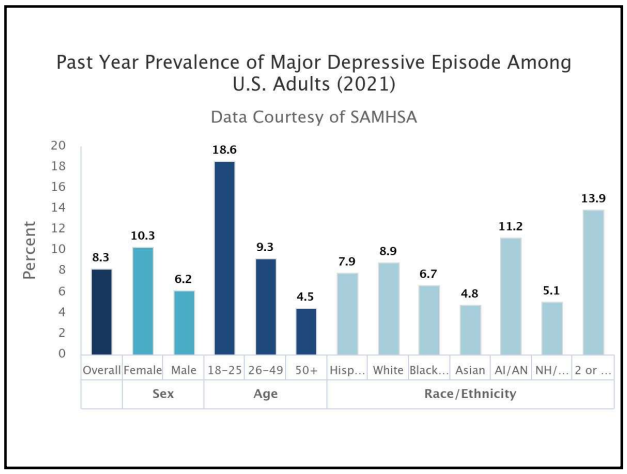
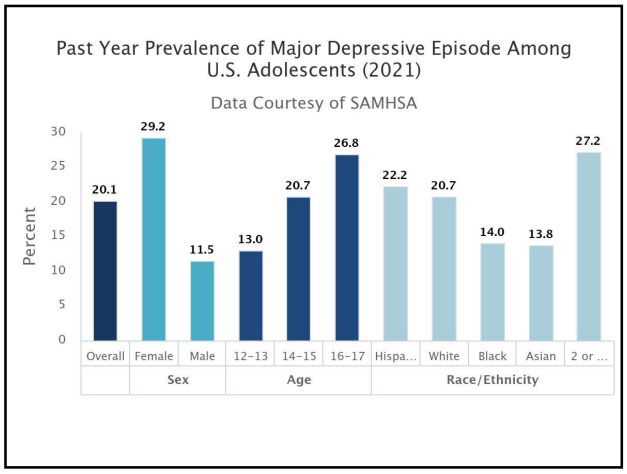
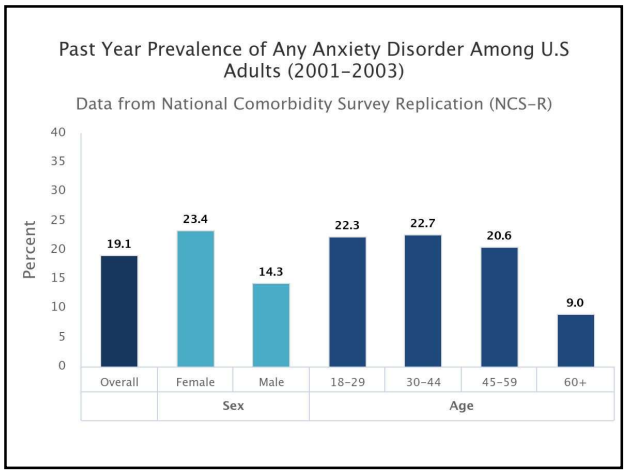

Past Year Prevalence of Major Depressive Episode Among U.S. Adults (2021)
Data Courtesy of SAMHSA
Percent
20
18
16
14
12
10
8
6
4
2
0
8.3
10.3
6.2
18.6
9.3
4.5
7.9
8.9
6.7
4.8
11.2
5.1
13.9
Overall
Female
Male
18–25
26–49
50+
Hisp...
White
Black...
Asian
AI/AN
NH/...
2 or ...
Sex
Age
Race/Ethnicity

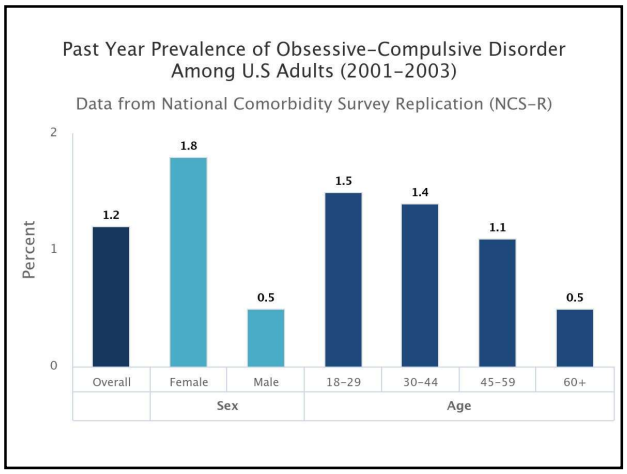
10


Past Year Prevalence of Major Depressive Episode Among U.S. Adolescents (2021)
Data Courtesy of SAMHSA
Percent
30
25
20
15
10
5
0
20.1
29.2
11.5
13.0
20.7
26.8
22.2
20.7
14.0
13.8
27.2
Overall
Female
Male
12–13
14–15
16–17
Hispa...
White
Black
Asian
2 or ...
Sex
Age
Race/Ethnicity

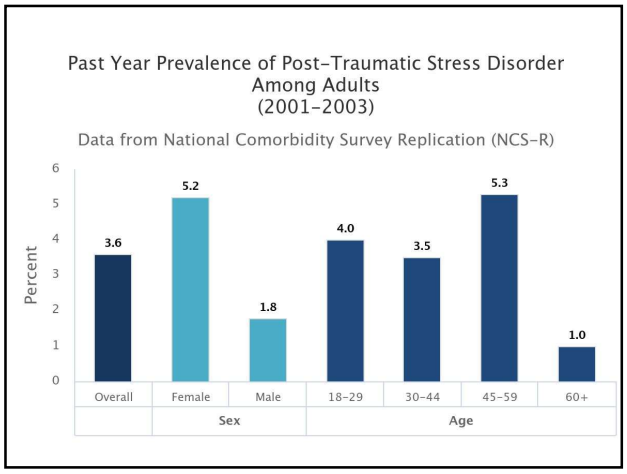
11


Past Year Prevalence of Any Anxiety Disorder Among U.S Adults (2001–2003)
Data from National Comorbidity Survey Replication (NCS-R)
Percent
40
35
30
25
20
15
10
5
0
19.1
23.4
14.3
22.3
22.7
20.6
9.0
Overall
Female
Male
18–29
30–44
45–59
60+
Sex
Age

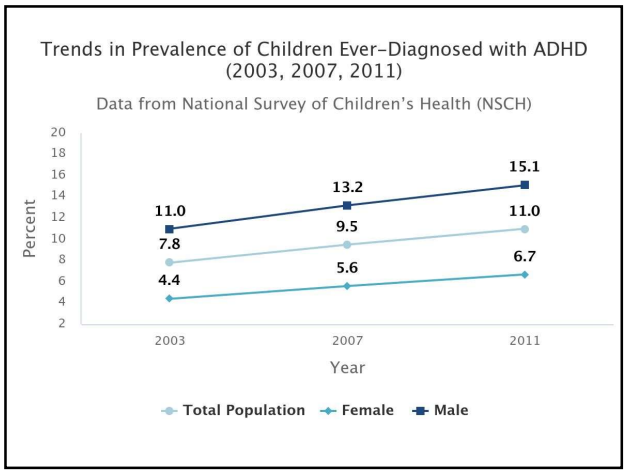
12


Past Year Prevalence of Obsessive-Compulsive Disorder Among U.S Adults (2001-2003)
Data from National Comorbidity Survey Replication (NCS-R)
Percent
2
1
0
1.2
1.8
0.5
1.5
1.4
1.1
0.5
Overall
Female
Male
18-29
30-44
45-59
60+
Sex
Age

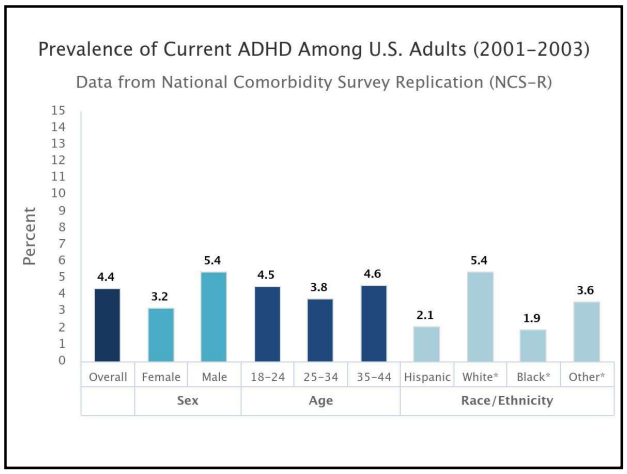
13


Past Year Prevalence of Post-Traumatic Stress Disorder Among Adults (2001-2003)
Data from National Comorbidity Survey Replication (NCS-R)
Percent
6
5
4
3
2
1
0
3.6
5.2
1.8
4.0
3.5
5.3
1.0
Overall
Female
Male
18-29
30-44
45-59
60+
Sex
Age

14


Trends in Prevalence of Children Ever-Diagnosed with ADHD (2003, 2007, 2011)
Data from National Survey of Children's Health (NSCH)
Percent
20
18
16
14
12
10
8
6
4
2
11.0
13.2
15.1
7.8
9.5
11.0
4.4
5.6
6.7
2003
2007
2011
Year
Total Population
Female
Male

15



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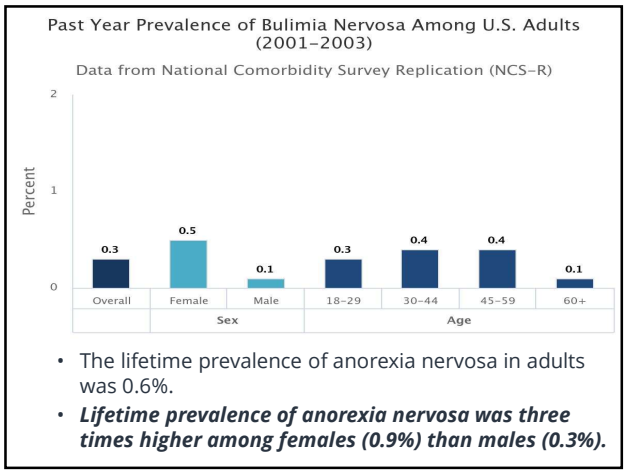
Eating Disorders

- Overall: W 3x > M
- Anorexia: 85-95% of cases are women
  - ….vs Manorexia
- Bulimia (
  - FDA-approved medication(s): _____
- Binge Eating Disorder: 65% of cases are women
  - FDA-approved medication(s): _____

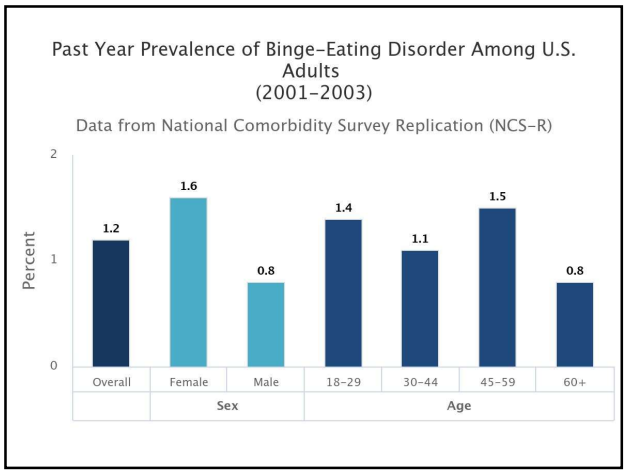
- Factors that contribute to the gender disproportionality of eating disorders are perceptions surrounding "thinness" in relation to success and sexual attractiveness and social pressures from mass media that are largely targeted towards women. Between males and females, the symptoms experienced by those with eating disorders are very similar such as a distorted body image.

17



- The lifetime prevalence of anorexia nervosa in adults was 0.6%.
- ***Lifetime prevalence of anorexia nervosa was three times higher among females (0.9%) than males (0.3%).***

18



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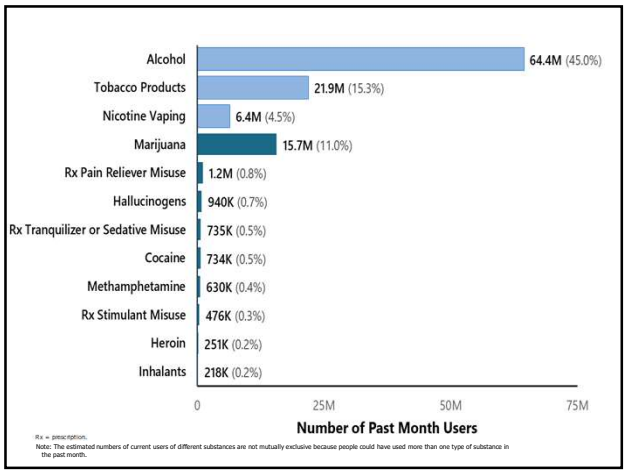
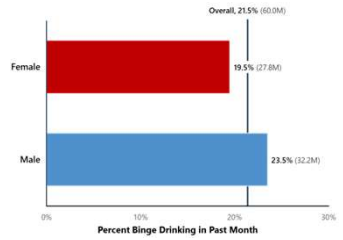
Substance Use

20



21

Binge Alcohol Use in the Past Month by Gender: Among People Aged 12 or Older



- Females were less likely to binge drink in the past month than Males

Note: Binge Alcohol Use is defined as drinking five or more drinks (for males) or four or more drinks (for females) on the same occasion on at least 1 day in the past 30 days.

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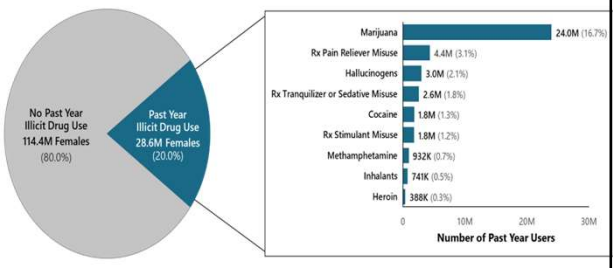
Past Year Illicit Drug Use: Among Females Aged 12 or Older



Rx = prescription.
Note: The estimated numbers of past year users of different illicit drugs are not mutually exclusive because people could have used more than one type of illicit drug in the past year.

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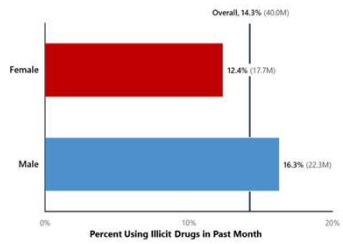
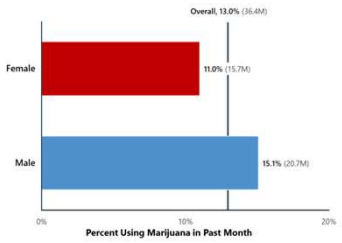
Illicit Drug Use in the Past Month by Gender: Among People Aged 12 or Older



- Females were less likely to use illicit drugs than Males

24

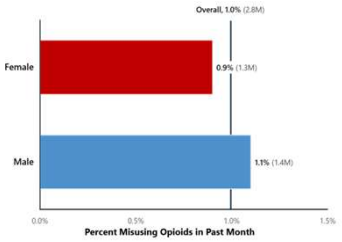
Marijuana Use in the Past Month by Gender:
Among People Aged 12 or Older



- Females were less likely to use marijuana than Males

25

Opioid Misuse in the Past Month by Gender:
Among People Aged 12 or Older



- No significant differences in prevalence of opioid misuse between Males and Females

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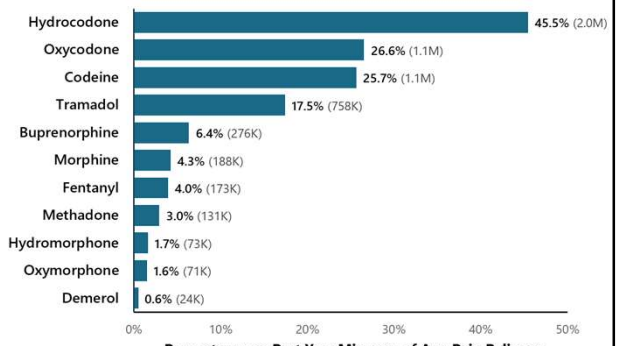
Past Year Prescription Pain Reliever Misuse: Among Females Aged 12 or Older Who Misused Any Prescription Pain Reliever



- In 2021, hydrocodone products were the most commonly misused subtype of prescription pain relievers

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Substance Use Disorder

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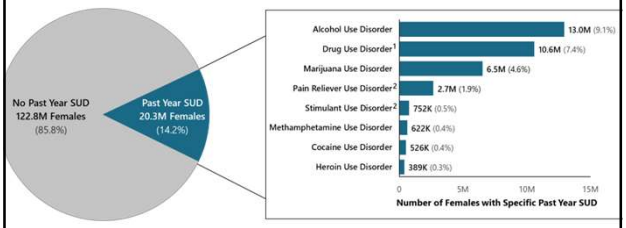
Past Year Substance Use Disorder (SUD):
Among Females Aged 12 or Older



Note: The estimated numbers of people with substance use disorders are not mutually exclusive because people could have use disorders for more than one substance.

[1] Includes data from all past year users of marijuana, cocaine, heroin, hallucinogens, inhalants, methamphetamine, and prescription psychotherapeutic drugs (i.e., pain relievers, tranquilizers, stimulants, or sedatives).

[2] Includes data from all past year users of the specific prescription drug.

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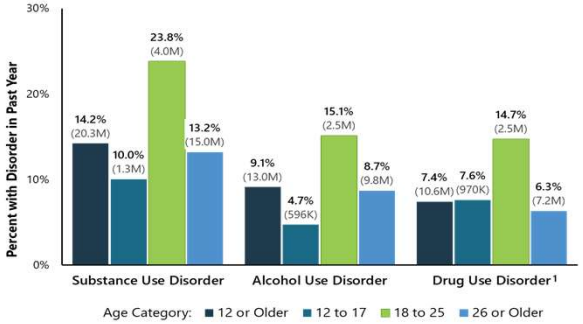
Past Year Substance Use Disorder:
Among Females Aged 12 or Older



- Female young adults aged 18 to 25 were the most likely to have a past year substance use disorder, alcohol use disorder, or drug use disorder

[1] Includes data from all past year users of marijuana, cocaine, heroin, hallucinogens, inhalants, methamphetamine, and prescription psychotherapeutic drugs (i.e., pain relievers, tranquilizers, stimulants, or sedatives).

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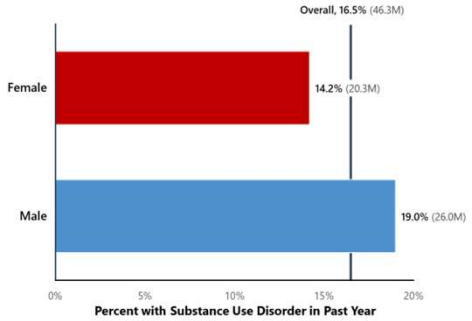
Substance Use Disorder in the Past Year by Gender: Among People Aged 12 or Older



- Females were less likely to have a substance use disorder than Males

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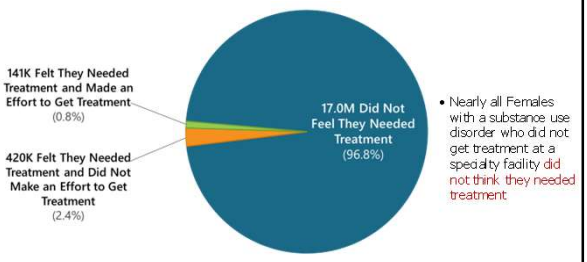
Perceived Need for Substance Use Treatment: Among Females Aged 12 or Older with a Past Year Illicit Drug or Alcohol Use Disorder Who Did Not Receive Substance Use Treatment at a Specialty Facility in the Past Year



- Nearly all Females with a substance use disorder who did not get treatment at a specialty facility did not think they needed treatment

17.5 Million Females with an Illicit Drug or Alcohol Use Disorder Who Did Not Receive Substance Use Treatment at a Specialty Facility

Note: People who had an illicit drug or alcohol use disorder were classified as needing substance use treatment.

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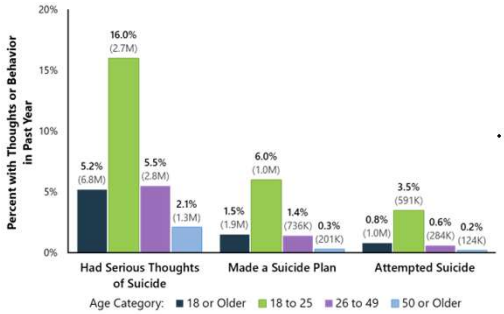
Past Year Serious Thoughts of Suicide, Suicide Plans, or Suicide Attempts: Among Female Adults Aged 18 or Older



- Thoughts of suicide, suicide plans, and suicide attempts were highest among Female young adults aged 18 to 25

Suicidality by Gender: Among Adults Aged 18 or Older: No differences were found for suicidality by gender

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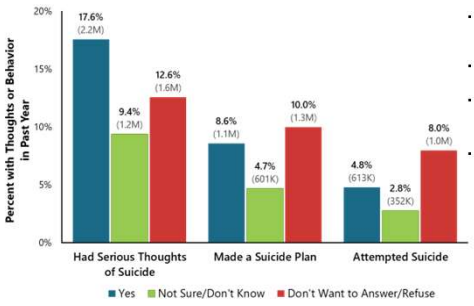
Past Year Serious Thoughts of Suicide, Suicide Plans, or Suicide Attempts: Among Female Adolescents Aged 12 to 17



- 17.6% of Female adolescents had thoughts of suicide
- 8.6% made a suicide plan
- 4.8% attempted suicide
- Many Female adolescents did not want to answer questions about suicide, which suggests that some Female adolescents could have had these thoughts but did not feel comfortable disclosing that information

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Factors affecting risk and presentations

- Some gender-specific risk factors that disproportionately affect women are income inequality, low social ranking, more child care, gender-based violence, and socioeconomic disadvantages.

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Other Factors affecting risk and presentations among the sexes

- _____
- _____
- _____
- _____
- _____
- _____

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Dosing, Metabolism and Clearance of Psychotropics

- Women
  - Greater % body fat with women (vs men)
  - Greater Vd for lipid-soluble drugs
    the sex-dependent disparities in lipophilic drug distribution may also increase with age
  - Smaller Vd for water-soluble drugs
  - Changing renal function
    - Pregnancy increases Lithium clearance
    - Common use of NSAIDs decrease Lithium clearance
- Men

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Gender Differences in Pharmacokinetics

Table 1. CYP450 Enzymes and Their Sex-Dependent Activity

CYP Enzyme	Enzyme Activity	Example Drugs	Other Characteristics
1A2	M > W	Clozapine, olanzapine	Suppressed activity during pregnancy
2A6	W > M	Nicotine, coumarin	Increased activity in female users of oral contraceptives
2B6	W > M	Bupropion, tamoxifen	Activity: Hispanic women > Caucasian or African-American women
2C9	M = W	Imipramine, phenytoin	Increased activity during pregnancy
2C19	M = W	Imipramine, topiramate	Decreased activity during pregnancy or use of oral contraceptives
2D6	Mostly W > M	Codeine, fluoxetine, haloperidol	Increased activity during pregnancy
3A4	Mostly W > M	Cyclosporine, erythromycin, nimodipine	Increased activity during pregnancy

M: men; W: women. Source: References 16-24.

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Table 2. Phase II Enzymes and Their Sex-Dependent Activity

Enzymes	Enzyme Activity	Example Drugs
UDP-glucuronosyltransferases (UGTs)	M > W	Oxazepam, acetaminophen
Sulfotransferases	M > W	Acetaminophen
N-acetyltransferases	M < W	Isoniazid, hydralazine
Methyltransferases	M > W	L-dopa, azathioprine

UDP: uridine diphosphate; M: men; W: women.
Source: References 16, 34, 37.

- Men show a faster clearance of drugs that are primarily eliminated by glucuronidation. ***Thus, oxazepam, metabolized mainly by UGT2B15, has a longer half-life in women than in men***
- https://www.uspharmacist.com/article/gender-differences-in-pharmacokinetics#:~:text=Sex%20differences%20in%20metabolism%20(phase,in%20men%20than%20in%20women.

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Gender Differences in Pharmacokinetics

- **Alcohol dehydrogenase**, the gastric mucosal enzyme responsible for alcohol oxidation, **is less active in women than in men**, *Therefore, women have higher peak blood concentration and subsequently faster absorption of alcohol after its consumption. They are also more susceptible to both acute and chronic effects of alcohol when compared to men*
- **Hepatic expression of Pgp is higher in men**, leading to faster transport and shorter elimination half-life of drugs including quinidine and digoxin, which are substrates of this transporter.

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Gender Differences in Pharmacokinetics

- *Excretion:* Both renal blood flow and glomerular filtration rate (GFR) are higher in men than in women. ***Therefore, women show a slower clearance of drugs that are actively eliminated via the kidney.***
- Examples of these drugs include digoxin, methotrexate, gabapentin, and pregabalin

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Gender Differences in Pharmacokinetics

- Pharmacokinetics of drugs can be significantly altered during ***pregnancy*** due to changes in drug distribution (increased plasma volume and total body water), absorption (prolonged gastric emptying), metabolism (changes in CYP and UGT activity), and excretion (increased GFR).
- As a result of preexisting conditions (e.g., epilepsy, hypertension) or pregnancy-related complications (e.g., gestational diabetes, severe nausea), a majority of pregnant women take at least one drug.
- As an example, pregnant women taking ***lamotrigine*** for epilepsy have shown increased seizures because the ***increased metabolism by UGT and subsequent faster clearance of lamotrigine during pregnancy*** have resulted in subtherapeutic drug concentrations.

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Gender Differences in Pharmacokinetics

- Furthermore, use of combined ***estrogen-progesterone oral contraceptives*** can have profound effects on pharmacokinetics by reducing the plasma albumin level, increasing or inhibiting the activity of CYP enzymes, and increasing the activity of UGTs.
- Therefore, it is important for clinicians to understand the pharmacokinetic changes of drugs during pregnancy or the use of oral contraceptives and properly readjust the dosage when necessary to avoid over- or underdosing female patients.

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A look at specific disorders

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Premenstrual Dysphoric Disorder (PMDD)

- **Timing of symptoms**

A) In the majority of menstrual cycles, at least 5 symptoms must be present in the final week before the onset of menses, start to improve within a few days after the onset of menses, and become minimal or absent in the week postmenses

- **Symptoms**

B) One or more of the following symptoms must be present:1) Marked affective lability (e.g., mood swings, feeling suddenly sad or tearful, or increased sensitivity to rejection)2) Marked irritability or anger or increased interpersonal conflicts
3) Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
4) Marked anxiety, tension, and/or feelings of being keyed up or on edge
C) One (or more) of the following symptoms must additionally be present to reach a total of 5 symptoms when combined with symptoms from criterion B above
1) Decreased interest in usual activities
2) Subjective difficulty in concentration
3) Lethargy, easy fatigability, or marked lack of energy
4) Marked change in appetite; overeating or specific food cravings
5) Hypersomnia or insomnia
6) A sense of being overwhelmed or out of control
7) Physical symptoms such as breast tenderness or swelling; joint or muscle pain, a sensation of "bloating" or weight gain

D) The symptoms are associated with clinically significant distress or interference with work, school, usual social activities, or relationships with others.

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FDA-approved Pharmacotherapy for PMDD

- Paroxetine *(continuous or intermittent)*
- Sertraline
- Fluoxetine (*as Sarafem*)
- Drospirenone & Ethinyl Estradiol

- *Note: allopregnanolone fluctuation during luteal phase has been implicated in PMDD in hormonally sensitive women. Allopregnanolone is a neurosteroid, a metabolite of progesterone and a positive allosteric modulator of GABA$_A$*

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Postpartum Depression

- Any antidepressant?
  - FLX, PAR, SERT, Nortriptyline: better studies

- Zulresso (IV)
- Zurzuvae (oral)

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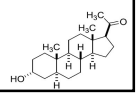
Brexanolone

- **Zulresso®** is first medication indicated for Post Partum Depression (PPD)
- **MoA**:
  - Allopregnanolone = naturally produced neuroactive steroid
  - Gamma-aminobutyric acid A ($GABA_A$) receptor positive allosteric modulator
- **Dose**: (100 mg/20 mL (5 mg/mL) single-dose vial)
  - ***60-hour inpatient infusion***
  - 0 to 4 hours: Initiate with a dosage of 30 mcg/kg/hour
  - 4 to 24 hours: Increase dosage to 60 mcg/kg/hour
  - 24 to 52 hours: Increase dosage to 90 mcg/kg/hour
  - 52 to 56 hours: Decrease dosage to 60 mcg/kg/hour
  - 56 to 60 hours: Decrease dosage to 30 mcg/kg/hour

- **ADRs:** Excessive Sedation / Loss of consciousness
- **BBW**: Suicidality



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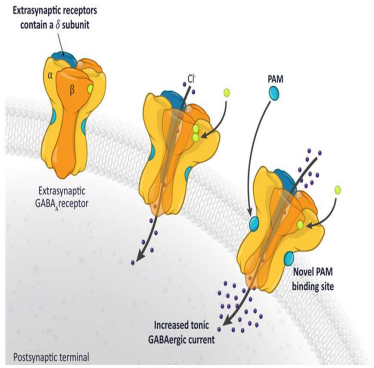

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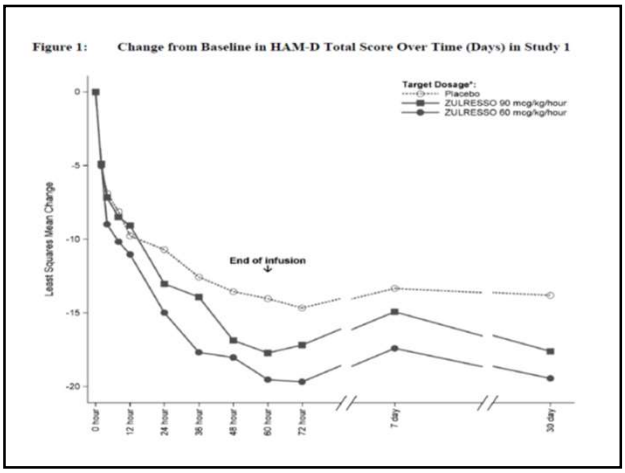

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Zuranolone

ZURZUVAE (zuranolone) capsules
20 mg • 25 mg • 30 mg

- **Zurzuvae®** is first oral medication indicated for Post Partum Depression
- **MoA**:
  - Gamma-aminobutyric acid A ($GABA_A$) receptor
    Positive Allosteric Modulator (PAM)
- **Dose**:
  - Recommended dosage is 50 mg orally once daily in the evening *with fat-containing food* **for 14 days**
- **ADRs:** Excessive Sedation / Loss of consciousness
- Most common adverse reactions (incidence ≥5% and greater than placebo) were somnolence, dizziness, diarrhea, fatigue, nasopharyngitis, and urinary tract infection.
- **BBW**: Caution while driving*

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BBW for Zuranolone

- ZURZUVAE causes driving impairment due to central nervous system (CNS) depressant effects.
- Advise patients not to drive or engage in other potentially hazardous activities until at least 12 hours after administration.
- Patients may not be able to assess their own driving competence or the degree of impairment caused by ZURZUVAE.

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Flibanserin (Addyi)

- **MoA**:
  - Demonstrates high affinity for the following serotonin (5-hydroxytryptamine or 5-HT) receptors: **agonist activity at 5-HT1A and antagonist activity at 5-HT2A.** Also has moderate antagonist activities at the 5-HT2B, 5-HT2C, and dopamine D4 receptors.
- **Dose**:
  - 100 mg administered orally once per day at bedtime.
  - ADDYI is dosed at bedtime because administration during waking hours increases the risks of hypotension, syncope, accidental injury, and central nervous system
- **ADRs:**
  - Most common adverse reactions (incidence ≥2%) are dizziness, somnolence, nausea, fatigue, insomnia, and dry mouth.
- **BBW**: Three*

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Flibanserin

ADDYI is indicated for the treatment of premenopausal women with acquired, generalized **hypoactive sexual desire disorder (HSDD)**, as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is NOT due to:

A co-existing medical or psychiatric condition,
Problems within the relationship, or
The effects of a medication or other drug substance.

Limitations of Use
ADDYI is not indicated for the treatment of HSDD in postmenopausal women or in men.
ADDYI is not indicated to enhance sexual performance.

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BBW for Flibanserin

- ***HYPOTENSION AND SYNCOPE IN CERTAIN SETTINGS***
- **Interaction with Alcohol**
- **The use of ADDYI and alcohol together close in time increases the risk of severe hypotension and syncope .**
- **Counsel patients to wait at least two hours after consuming one or two standard alcoholic drinks before taking ADDYI at bedtime or to skip their ADDYI dose if they have consumed three or more standard alcoholic drinks that evening.**
- **Contraindicated with Strong or Moderate CYP3A4 Inhibitors**
- **The concomitant use of ADDYI and moderate or strong CYP3A4 inhibitors increases flibanserin concentrations, which can cause severe hypotension and syncope. Therefore, the use of moderate or strong CYP3A4 inhibitors is contraindicated in patients taking ADDYI.**
- **Contraindicated in Patients with Hepatic Impairment**
- **The use of ADDYI in patients with hepatic impairment increases flibanserin concentrations, which can cause severe hypotension and syncope Therefore, ADDYI is contraindicated in patients with hepatic impairment.**

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First Generation Antipsychotics (FGAs)

Chlorpromazine	Thorazine	1958
Trifluoperazine	Stelazine	1958
Perphenazine	Trilafon	1958
Thioridazine	Mellaril	1959
Fluphenazine	Prolixin	1959
Thiothixene	Navane	1967
Haloperidol	Haldol	1967
Loxapine*	Loxitane	1973
Molindone*	Moban	1974

Tenth FGA, practically never used for schizophrenia despite FDA-approval?

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Atypical Antipsychotics (SGAs)

Clozapine	Clozaril	Novartis	1990
Risperidone	Risperdal	Janssen	1994
Olanzapine	Zyprexa	Lilly	1995
Quetiapine	Seroquel	Zeneca	1997
Ziprasidone	Geodon	Pfizer	2001
Aripiprazole	Abilify	BMS/Otsuka	2002
Paliperidone	Invega	Janssen	2007
Illoperidone	Fanapt	Novartis	2009
Asenapine	Saphris	Merck	2009
Lurasidone	Latuda	Sunovion	2010
Brexpiprazole	Rexulti	Otsuka	2015
Cariprazine	Vraylar	Allergan	2015
Lumateperone	Caplyta	ITCI	2019
Olanzapine+ Samidorphan	Lybalvi	Alkermes	2021

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Antidepressant Selection and Treatment

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Historical, Research & Clinical Applications of *'Antidepressants'*

- ***Depression***
- **Obsessive-Compulsive Disorder**
- **Panic Disorder**
- **Social Anxiety Dis.**
- **Generalized Anxiety Disorder**
- **PMDD (PMS)**
  - ***VMS assoc. with menopause***
- **Post-traumatic Stress Disorder (PTSD)**
- **Substance Use Disorders**
- **Eating Disorders**
- **Chronic Headache**
- **Chronic Pain Syndromes**
- **Impulse Control / Autism**

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The Available Antidepressants

- Amitriptyline
- Imipramine
- Doxepin
- Nortriptyline
- Desipramine
- Protriptyline
- Clomipramine
- ***Maprotiline****
- Amoxapine
- Duloxetine
- Fluoxetine / Sertraline / Paroxetine
- Fluvoxamine / Citalopram / Escitalopram
- Trazodone / Nefazodone
- Bupropion / Mirtazapine
- Venlafaxine / Desvenlafaxine
- Selegiline / Phenelzine / Tranycypromine
- Vilazodone / Vortioxetine
- Levomilnacipran
- **Esketamine**
- **Bupropion+Dextromethorphan**
- ***Brexanolone / Zuranolone****

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Antidepressant Selection Criteria

Primary Criteria:

- Patient's history of response
- Family history of response
- Patient's medical status / Age
- Side effect profile
- Patient's clinical presentation

- ***Other Secondary Criteria***

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Antidepressant Selection Criteria

Secondary Criteria:

- Patient's concomitant medications
  - Drug-Drug / Drug-Food Interactions
- Cost
- Compliance / Adherence issues
- Dosing Regimen / Formulations
- Stigma, reputation of the drug, media

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Challenges to Treatment

- Recognition of Depression
  - Worsening after treatment
- Co-Morbid Illnesses
  - Matching treatments
- Medication Compliance
- Side Effect Profiles of Antidepressants
- Direct and Indirect Costs of Treatment
- **Treatment Resistance / Partial Response**

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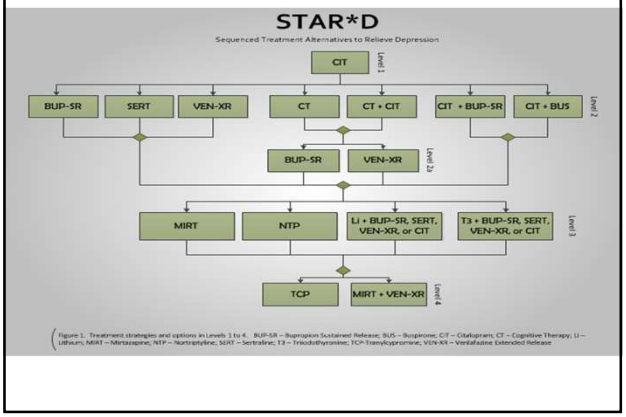

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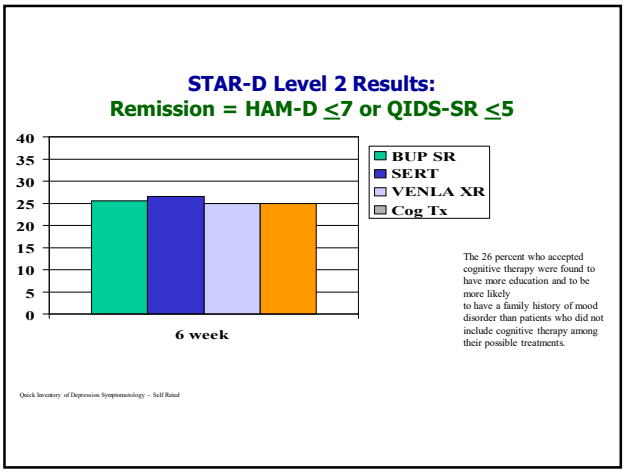

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Options for the Treatment of the Severe or Refractory Patient

- **Combination of Antidepressants:**
  - Use agents having two (2) or more mechanism of actions
  - Use two different and selective acting antidepressants
  - Symbyax™ (Olanzapine+Fluoxetine) is FDA-approved for TRD
- **Adjunctive therapy:**
  - ***Atypical Antipsychotic Agents****
  - Mood Stabilizers?, Could it actually be a type of bipolar disorder?
  - Thyroid augmentation, Buspirone, Pindolol, Psychostimulants
  - ***Esketamine NS*** is FDA-approved for TRD

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Bipolar-Depression

- **Difficult to diagnose**:
  - Often misdiagnosed as……
- **Some features / indicators for BD**:
  - Family hx. of bipolar disorder
  - Hx. of antidepressant-induced mania or hypomania
  - Early age of onset
  - Recurrent pattern of illness
  - Atypical sx: hypersomnia, hyperphagia
  - Psychotic sx
  - Lack of response to AD tx.
  - Abrupt onset and ending of sx.

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Bipolar-Depression

Symptomatic Time:

- Spent in Depressed phase: **67.8%**
- Spent in Mania / hypomania: 19.7%
- Spent in Rapid cycling / mixed states: 12.5%

- ***Problem:***
  - ***Antidepressants are no more effective than Placebo in treating Bipolar Depression***

Sachs GS, et.al., NEJM. 2007; 356:1711-1722

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Bipolar-Depression

The medications that are FDA-approved:

- _____
- _____
- _____
- _____
- _____

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Lurasidone (Latuda™)

- FDA approved for the acute treatment of schizophrenia in adults
  - Approved Oct. 28, 2010
  - ***Approved July, 2013 for Bipolar-Depression***
- Pharmacology
  - Exerts actions via combination blockade of D_2 & 5-HT_2 receptors (5-HT_2 > D_2)
  - Moderate receptor affinity for α_1 receptors
  - Low affinity for histamine receptors
  - No activity at cholinergic receptors
  - **40 – 160 mg/day**

Scott LJ. Roperidone: in schizophrenia. *CNS Drugs* 2009;23(10):887-90.

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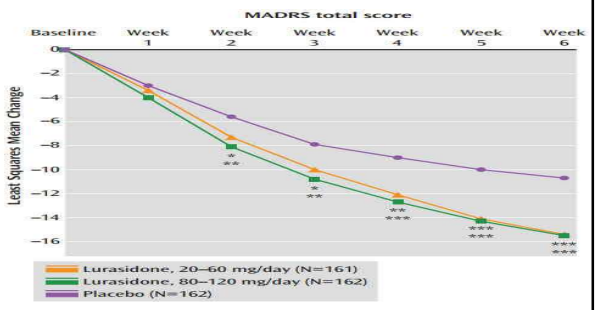
Bipolar-Depression Results



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Adjunctive Treatments for Resistant or Partial Responders to Antidepressants for Unipolar Major Depression

The medications that are FDA-approved:

- _____
- _____
- _____
- _____
- _____* (for TRD)
- _____* (for TRD)

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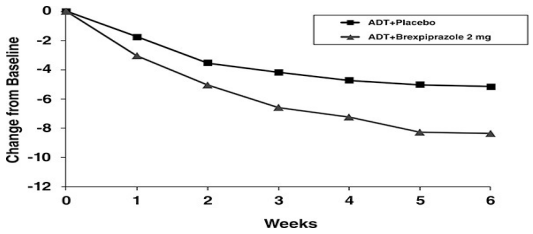
Brexpiprazole (as Adjunct): MADRS score reduction



23.2% of the patients receiving brexpiprazole were responders, vs 14.5% for placebo, yielding a NNT of 12 (95% CI, 8-26);
14.4% of the brexpiprazole-treated patients met remission criteria, vs 9.6% for placebo, resulting in a NNT of 21 (95% CI, 12-138).[6]

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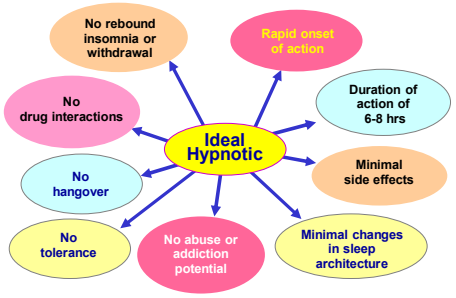
Pharmacological Management of Insomnia



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Insomnia prevalence between sexes.

Age	Insomnia present (%)		Total	Insomnia absent (%)		Total
	Female	Male		Female	Male	
≤35	20 (69)	9 (31)	29	49 (56)	38 (44)	87
≥36	43 (68)	20 (32)	63	68 (69)	31 (31)	99
Total	63	29		117	69	

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FDA-Approved Treatments for Insomnia

Benzodiazepines
- Temazepam (Restoril®)
- Flurazepam (Dalmane®)
- Triazolam (Halcion®)
- Quazepam (Doral®)
- Estazolam (Prosom®)

Melatonin-Receptor agonists
- Ramelteon (Rozerem®)
- Tasimelteon (Hetlioz®)
- Melatonin*

- **BZD_1-Receptor agonists**
  - Zolpidem (Ambien®)
  - Zaleplon (Sonata®)
  - Eszopiclone (Lunesta®)
- **Histamine antagonists**
  - Doxepin (Silenor®)
  - Diphenhydramine
- **Dual Orexin Receptor Antagonists (DORAs)**
  - Suvorexant (Belsomra®)
  - Lemborexant (Dayvigo®)
  - Daridorexant (Quiviviq®)

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Summary

- Differences do exist between the sexes for the risks and prevalence rates of mental disorders and substance use disorders.
- Consider pharmacokinetic differences and changes in PKs between the sexes.
- Recent FDA-approvals of specific medications that are related to sex-specific conditions should be considered, and more research is needed in gender studies.

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